Annual Report 2013

ciberer

CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED DE ENFERMEDADES RARAS

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1 Organization

Letter from the Scientific Director

In 2013, the Centre for Biomedical Network Research on Rare Diseases (CIBERER) continued down the path it has been on for the last few years, securing its position as a national leader in research on Rare Diseases (RD), undoubtedly due to the collaboration of the different research Centers and groups making up CIBERER and of all the investigators working in and collaborating with it. CIBERER is now responsible for meeting the needs involved with being a Center of excellence of such characteristics and the upcoming challenges in the field of RD in the coming years.

In 2013, CIBERER instituted the scientific guidelines necessary for aligning itself both on a national level with the 2013-2016 State Plan for Scientific, Technical and Innovation Research, and on an European level with the new European Commission Horizon 2020 R&D&I Programme, in which the treatment, diagnosis and awareness of rare diseases continues to be a priority. These problems are approached internationally through the objectives of the "International Rare Disease Research Consortium" (IRDiRC). Its two objectives are essentially to develop 200 new therapies for rare diseases in 2020 and to be able to diagnose most of them. In this national and international context, and as a response to these proposed needs, CIBERER conducts its activities fully complying with national and international policies in the field of Rare Diseases.

2013 was the best year for CIBERER as regards scientific production. The number of citable papers this year increased by 16% with respect to 2012, going from 9.61 to 10.45 per group. According to data available in April 2014, 673 CIBERER papers were published. If this figure, which only includes citable documents, is combined with the meeting abstracts included in WoS, that figure amounts to 786 publications, 100 more than the previous year.

In relation to the CIBERER Programme "Genes of Undiagnosed Rare Diseases", an enormous project for the application of exome sequencing to a number of RD, the identification of mutations in 26 genes not previously associated with the pathology under study and the identification of new mutations in 22 genes that are already known and were associated with that disease stand out as an overall result, pending the validation result of many candidate genes. The first results published in international journals were obtained from this work, particularly during 2013. Since the programme started, CIBERER groups have published 10 original papers in international journals and 6 other papers are currently being reviewed by the editors for acceptance. Furthermore, there are 3 other studies that have ended and the 3 manuscripts are currently being prepared. This programme was the basis for implementing in 2014 the CIBERER Exome Server and the SPANEX project which will provide an exome database and genetic information about the Spanish population.

CIBERER furthermore enhanced several translational initiatives between in 2013, particularly the association of clinical groups. This action will allow CIBERER groups to collaborate with groups that have vast clinical experience in RD, accelerating the definitive translation of the research that is being conducted to the National Health System. In 2013, four clinical groups from the Pediatric and Developmental Medicine Programme with considerable clinical research experience and that complement the partial lack of clinical geneticists and dysmorphologists in the CIBERER joined. Following a similar process, at the end of 2013 the process for clinical groups to join from the Inherited metabolic Medicine Programme began at the end of 2013 and the appropriate agreements will be signed in 2014.

CIBERER, as a Spanish and European reference Center in scientific research on the biological and pathological basis of RD, has also stood out in 2013 for its participation in international initiatives such as ORPHANET, the EU Committee of Experts on RD (EUCERD) and the EUCERD Joint Action, the European project EUROPLAN, the Inter-

national Rare Diseases Research Consortium IRDiRC, as well as its participation in projects funded by the European Commission for the development of European networks on metabolic diseases, E-IMD and E-HOD.

2013 was officially declared the "Spanish Year of Rare Diseases" by the Ministry of Health, Social Services and Equality. This initiative seeks to make citizens aware of these pathologies and to spark the interest of investigators, professionals and the industry, and its focus point lies in health, scientific and social perspective. CIBERER actively participated by organizing activities under that motto, such as organizing two International Symposiums together with the Ramón Areces Foundation (one on Mitochondrial Diseases and the other on Intellectual Impairment), organizing the 4th edition of the "DNA Day CIBERER Workshop" or the 5th CIBERER Conference "To conduct research is to move forward (Investigar es Avanzar)".

The Scientific Report herein presented is the summary of what the CIBERER has contributed to advancement in biomedical research and translation in RD, which is the primary target of our efforts, this year. I cannot end this letter without first expressing gratitude for the support offered by the groups making up the CIBERER and the team of scientific managers, without whom all these achievements and the holding of our institution in a state-of-the-art position in the scientific panorama would have been impossible. From here I would like to express our commitment to continue conducting quality research for the benefit of people suffering rare diseases as well as their families.

Prof. Francesc Palau

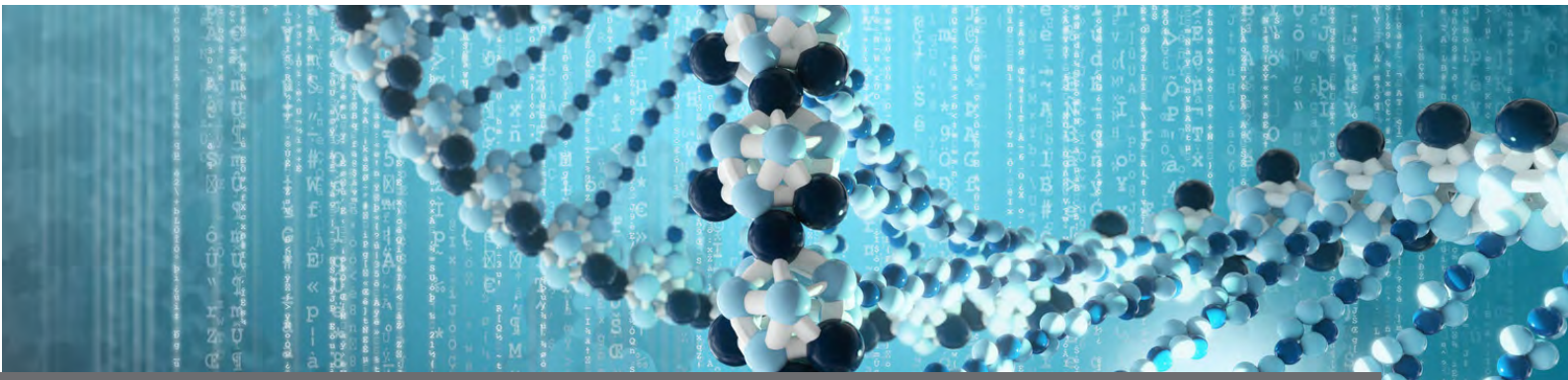
Scientific Director of the CIBERER

List of CIBERER Groups 2013

CIBERER Unit	Group Leader	Center – Institution	AUTON. COMM.
U701	Dr. Ramón Martí Seves	Unitat de Patologia Mitocondrial i Neuromuscular, Hospital Universitari Vall d'Hebron-Institut de Recerca, Institut Català de la Salut, Barcelona.	Cataluña
U702	Dr. Guillermo Antiñolo	Unidad de Gestión Clínica de Genética, Reproducción y Medicina Fetal, Hospital Universitario Virgen del Rocío, Fundación Pública Andaluza para la Gestión de la Investigación en Salud, Sevilla.	Andalucía
U703	Dr. Rafael Artuch	Laboratorio de Enfermedades Metabólicas, Hospital Sant Joan de Déu, Barcelona.	Cataluña
U704	Dr. Carmen Ayuso	Servicio de Genética, ISS-Fundación Jiménez Díaz, Madrid.	Madrid
U705	Dr. Eduardo Tizzano Ferrari	Servicio de Genética, Instituto de Investigación Hospital de la Santa Creu i Sant Pau, Barcelona.	Cataluña
U706	Dr. Javier Benítez	Programa de Genética del Cáncer Humano, Fundación Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid.	Madrid
U707	Dr. Carmelo Bernabéu	Patología vascular y receptores endoteliales, Centro de Investigaciones Biológicas, CSIC, Madrid.	Madrid
U708	Dr. Juan Bernal	Hormonas tiroideas y cerebro, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid.	Madrid
U709	Dr. Paola Bovolenta	Morfogénesis y Diferenciación del Sistema Nervioso de Vertebrados, Centro de Biología Molecular "Severo Ochoa" (CBMSO). CSIC-UAM., Universidad Autónoma de Madrid, Madrid.	Madrid
U710	Dr. Juan Antonio Bueren	División de Terapias Innovadoras en el Sistema hematopoyético, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid.	Madrid
U711	Dr. Ángel Carracedo	Group de Medicina Xenómica, Facultad de Medicina, Universidad de Santiago de Compostela, A Coruña.	Galicia
U712	Dr. Antonio Carrascosa	Servicio de Pediatría, Hospital Universitari Vall d'Hebron-Institut de Recerca, Institut Català de la Salut, Barcelona	Cataluña
U713	Dr. José M. Cuezva	La mitocondria y su disfunción en patología, Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid.	Madrid
U714	Dr. Marcela del Río Nechaevsky	Unidad de Medicina Regenerativa (CIEMAT) y Departamento de Bioingeniería (UC3M), Unidad Mixta de Investigación CIEMAT y Universidad Carlos III de Madrid, CIEMAT-UC3M, Madrid.	Madrid
U715	Dr. Joaquín Dopazo	Departamento de Bioinformática y Genómica, Centro de Investigación Príncipe Felipe , Fundación Centro de Investigación Príncipe Felipe (CIPF), Valencia.	Com. Valenciana
U716	Dr. Cristina Fillat	Laboratori de Teràpia Gènica, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona.	Cataluña
U717	Dr. Rafael Garesse	Departamento de Bioquímica, Laboratorio B19, Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, Facultad de Medicina UAM, Madrid.	Madrid

CIBERER Unit	Group Leader	Center – Institution	AUTON. COMM.
U718	Dr. Roser González Duarte	Genètica Molecular Humana, Departament de genètica. Facultat de Biologia, Universitat de Barcelona, Barcelona.	Cataluña
U719	Dr. Eduard Gratacòs	Group de Investigación en Medicina Fetal y Perinatal. Servicio de Medicina Materno Fetal, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona.	Cataluña
U720	Dr. Daniel Grinberg	Departamento de Genética, Genética Molecular Humana, Facultat de Biología, Universitat de Barcelona, Barcelona.	Cataluña
U721	Dr. Erwin Knecht	Laboratorio de Degradación Intracelular de Proteínas y Enfermedades Raras, Centro de Investigación Príncipe Felipe, Fundación Centro de Investigación Príncipe Felipe (CIPF), Valencia.	Comunidad Valenciana
U722	Dr. Francesc Cardellach	Patología Mitocondrial, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona.	Cataluña
U723	Dr. Miguel Á. Martín Casanueva	Laboratorio de Enfermedades Mitocondriales y Neuromusculares, Hospital Universitario 12 de Octubre, Servicio Madrileño de Salud, Madrid.	Madrid
U724	Dr. Mª Luisa Martínez-Frías	Centro de Investigación sobre Anomalías Congénitas - CIAC, Centro mixto ISCIII - ASEREMAC, Madrid.	Madrid
U725A	Dr. Luis Castaño	Group de investigación en Endocrinología y Diabetes, Hospital de Cruces, Fundación Vasca de Innovación de Investigaciones Sanitarias, Vizcaya.	País Vasco
U726	Dr. Montserrat Milà	Group de Investigación en Genética de Enfermedades Raras (GICER), Hospital Clinic GICER (Servicio de Bioquímica y Genética Molecular), Corporació Sanitária Clínic, Barcelona.	Cataluña
U727	Dr. Julio Montoya	Departamento de Bioquímica y Biología Molecular y Celular, Facultad de Veterinaria, Universidad de Zaragoza, Zaragoza.	Aragón
U728	Dr. Miguel A. Moreno Pelayo	Servicio de Genética, Hospital Ramón y Cajal, Servicio Madrileño de Salud, Madrid.	Madrid
U729	Dr. Plácido Navas	Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide-CSIC, Sevilla.	Andalucía
U730	Dr. Virginia Nunes	Centro de Genética Médica y Molecular CGMM, CGMM-IDIBELL Hospital Duran y Reynals, Fundació IDIBELL, Barcelona	Cataluña
U731	Dr. Manuel Palacín	Institut de Recerca Biomèdica, Fundaciò Privada Institut de Recerca Biomèdica, Barcelona.	Cataluña
U732	Dr. Francesc Palau	Programa de Enfermedades Raras y Genéticas, Centro de Investigación Príncipe Felipe, Fundación Centro de Investigación Príncipe Felipe, Valencia.	Comunidad Valenciana
U733	Dr. Federico Pallardó	Departamento de Fisiología, Facultat de Medicina, Universitat de València, Valencia.	Comunidad Valenciana
U734	Dra. Consuelo González Manchón	Fisiopatología de trastornos hemostáticos; Bases celulares y moleculares de la enfermedad de Alzheimer y otras demencias, Centro de Investigaciones Biológicas, CSIC, Madrid.	Madrid
U735	Dr. Luis Pérez Jurado	Unidad de Genética, Facultad de Ciencias Experimentales y de la Salud, Universitat Pompeu Fabra, Barcelona.	Cataluña
U737	Dr. Antonia Ribes	Enfermedades Metabólicas Hereditarias, Institut de Bioquímica Clínica y Genética Molecular, Corporació Sanitària Clínic, Barcelona.	Cataluña
U738	Dr. Santiago Rodríguez de Córdoba	Patología Molecular y Genética del Complemento, Centro de Investigaciones Biológicas, CSIC, Madrid.	Madrid
U739	Dr. Vicente Rubio	Enzimopatología estructural, Instituto de Biomedicina de Valencia, CSIC, Valencia.	Comunidad Valenciana
U740	Dr. Eduardo Salido	Departamento de Anatomía Patológica, Patología Molecular, Hospital Universitario de Canarias, Fundación Canaria Rafael Clavijo, Tenerife.	Islas Canarias

CIBERER Unit	Group Leader	Center – Institution	AUTON. COMM.
U741	Dr. Francisca Sánchez Jiménez	Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Universidad de Málaga, Málaga.	Andalucía
U742	Dr. Pascual Sanz	Unidad de Señalización por Nutrientes, Instituto de Biomedicina de Valencia, CSIC, Valencia.	Comunidad Valenciana
U743	Dr. Jorgina Satrústegui	Departamento de Biología Molecular, Centro de Biología Molecular "Severo Ochoa" (CBMSO), CSIC-UAM Universidad Autónoma de Madrid, Madrid.	Madrid
U744	Dr. José Serratosa	Laboratorio de Neurología, IIS-Fundación Jiménez Díaz, Madrid.	Madrid
U745	Dr. Jordi Surrallés	Departamento de Genética y Microbiología, Universitat Autònoma de Barcelona, Barcelona.	Cataluña
U746	Dr. Belén Pérez González	Centro de Investigación y Diagnóstico Enfermedades Metabólicas Hereditarias, Centro de Biología Molecular "Severo Ochoa"(CBMSO), Universidad Autónoma de Madrid, Madrid.	Madrid
U747	Dr. Susan Webb	Enfermedades de la hipófisis. Departamento Medicina, Servicio de Endocrinología, Instituto de Investigación Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona.	Cataluña
U748	Dr. Javier Díaz Nido	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid.	Madrid
U749	Dr. José Fernández Piqueras	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid.	Madrid
U750	Dr. Raúl Estévez Povedano	Departamento de Ciencias Fisiológicas II, Facultat de Medicina, Universitat de Barcelona, Barcelona.	Cataluña
U751	Dr. Cecilio Giménez Martín	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid.	Madrid
U752	Dr. Pilar Giraldo	Group de estudio de enfermedad de Gaucher y neoplasias hematológicas. Servicio Hematología, Hospital Universitario "Miguel Servet", Instituto Aragónés de Ciencias de la Salud, Zaragoza.	Aragón
U753	Dr. Pablo D. Lapunzina Badía	INGEMM-Instituto de Genética Médica y Molecular , Hospital Universitario "La Paz", Servicio Madrileño de Salud, Madrid.	Madrid
U754	Dr. Margarita López Trascasa	Diagnóstico y caracterización de alteraciones del sistema del complemento, Unidad de Inmunología y Unidad de Investigación. Hospital Universitario "La Paz", Servicio Madrileño de Salud, Madrid.	Madrid
U755	Dr. José María Millán Salvador	Unidad de Genética, Hospital Universitario La Fe, IIS-Hospital La Fe, Valencia.	Comunidad Valenciana
U756	Dr. Lluís Montoliu José	Modelos animales por manipulación genética, Centro Nacional de Biotecnología (CNB), CSIC, Madrid.	Madrid
U757	Dra. Rosario Perona	Laboratorio de terapias de enfermedades con defectos en telomerasa, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid.	Madrid
U758	Dr. Manuel Posada de la Paz	Instituto de Investigación en Enfermedades Raras (IIER), Instituto de Salud Carlos III, Madrid.	Madrid
U759	Dr. Aurora Pujol Onofre	Laboratorio de enfermedades neurometabólicas, Institut d´Investigació Biomèdica de Bellvitge IDIBELL-Hospital Duran i Reynals, IDIBELL, Barcelona.	Cataluña
U760	Dr. Victor Luis Ruiz Pérez	Group de Genética Humana y Patología Molecular, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid.	Madrid
U761	Dr. Isabel Varela Nieto	Group de Neurobiología de la Audición, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM, Madrid.	Madrid



Organizational Structure

The CIBERER is formed by 60 Research groups, belonging to numerous types of institutions: University Hospitals, Universities, Public Research Bodies, such as the Carlos III Health Institute (ISCIII), the Spanish Council for Scientific Research (CSIC) and the Energy, Environmental and Technological Research Center (CIEMAT), and Autonomous Community Research Centers. Each of these groups is a CIBERER unit.

CIBERER comprises a large team consisting of over 700 people, many of whom are CIBERER staff investigators, and the rest are members of the personnel attached to the CIBERER. This team consists of basic and clinical biomedical investigators, research technicians and management staff.

As a public consortium, CIBERER is governed by a Governing Board and a Permanent Commission (administration and steering bodies) in which the 29 Institutions belonging to the CIBERER participate. The organizational structure consists of Scientific Management under Dr. Francesc Palau which, together with a Steering Committee, coordinates the activity of the 7 research programmes (RPs) into which the CIBERER groups are distributed. The CIBER Management Office offers the administrative support necessary for operation of the Institution.

Organizational Structure

Steering Committee		
Scientific Director		Dr. Francesc Palau
Scientific Assistant Director		Dr. José María Millán
Research Programme Coordinators		
Medical Programmes	Genetic Medicine	Dr. Guillermo Antiñolo
	Inherited Metabolic Medicine	Dra. Antonia Ribes
	Mitochondrial Medicine	Dr. Miguel A. Martín
	Pediatric and Developmental Medicine	Dr. Pablo Lapunzina
	Sensorineural Pathology	Dr. Carmen Ayuso
	Endocrine Medicine	Dr. Susan Webb
	Hereditary Cancer and Related Syndromes	Dr. Jordi Surrallés
Training Programme		Dr. Luis Pérez Jurado

2013 Budget

To be implemented with funds from the ISCIII (Carlos III Health Institute) and the balance left over from previous fiscal years

Revenues	2013 Budget
Surplus from a registered grant from the previous fiscal year	1.810.385,19
Registered grant from the fiscal year	4.930.610,00
Financial revenues	10.000,00
Balance left over from previous fiscal years	489.815,12
TOTAL FUNDS	7.240.810,31
BUDGET RESERVE FOR 2013 E-RARE CALL FOR PROPOSALS	500.000,00
TOTAL FUNDS AVAILABLE	6.740.810,31

Revenues	2013 Budget
Research Programmes: Rare Disease Programmes	4.708.865,31
Rp1- Genetic Medicine	1.059.553,05
Rp2- Inherited Metabolic Medicine	956.830,87
Rp3- Mitochondrial Medicine	628.782,25
Rp4- Pediatric and Developmental Medicine	713.425,81
Rp5- Sensorineural Pathology	570.972,37
Rp6- Endocrine Medicine	128.006,50
Rp7- Hereditary cancer and Related Syndromes	651.294,46
Transversal Instrument Platforms for RD	672.601,14
PITER I- Health Services and Products for RD	30.000,00
PITER II- RD Research Support Platforms	330.842,70
PITER III- Training in RD	311.758,44
Research Support Tools	1.022.230,67
HAI I.- Project and Programme Management	158.376,60
HAI II.- Communication Plan	167.500,00
HAI III.- Internationalization	15.000,00
HAI IV.- Strategic Alliances	120.000,00
HAI V.- Management Office	323.854,07
HAI VI.- Governing and Advisory Body Expenses	47.500,00
HAI VII.- Overhead and Structural Costs	190.000,00
TOTAL BUDGET EXPENSES AND INVESTMENTS	6.403.697,12

To be implemented with public and private funds

Revenues	2013 Budget
Other public revenues	1.087.356,46
Private revenues	419.189,62
TOTAL FUNDING FOR THESE ACTIVITIES	1.506.546,08

Revenues	2013 Budget
Transversal Instrument Platforms for RD	177.791,86
PITER I- Health Services and Products for RD	97.180,83
PITER II- RD Research Support Platforms	61.711,03
PITER III- Training in RD	18.900,00
Research Support Tools	330.159,61
HAI II.- Communication Plan	3.462,61
HAI IV.- Strategic Alliances	326.697,00
Other research projects:	998.594,61
Rp1- Genetic Medicine	343.160,81
Rp2- Inherited Metabolic Medicine	63.145,38
Rp3- Mitochondrial Medicine	199.055,89
Rp4- Pediatric and Developmental Medicine	48.700,00
Rp5- Sensorineural Pathology	102.567,00
Rp6- Endocrine Medicine	57.000,00
Rp7- Hereditary Cancer and Related Syndromes	184.965,53
TOTAL BUDGET EXPENSES AND INVESTMENTS	1.506.546,08

2 Scientific Programmes

The basic structure of CIBERER consists of Research Programmes (RPs) which allow grouping CIBERER units according to their areas of scientific interest. Organizing into RPs allows optimizing resource allocation, strengthening research groups, promoting scientific, technical and clinical collaboration to improve scientific results and obtain a higher degree of compliance with the proposed strategic objectives.

CIBERER programme structuring is complex, largely due to the idiosyncrasy inherent to the field of RD, the field of medicine and the field of public health which covers over 7,000 diseases, mainstreaming all human organic systems. To scientifically, logically and operatively solve this complexity, an approach was chosen in which the RPs are supported by biomedical research instruments, specifically by Biomedical Intramural Projects for RD (PIBER) and by Transverse Instrument Support Platforms for RD (PITER).

The objective of the RPs is to organize the groups based on the large medical areas in which the groups conduct their research. Conceptually speaking, 7 programmes are considered taking into account the fundamental biological and historical aspect characterizing each RD either separately or as a classified group of diseases:

- **Genetic Medicine Programme**
- **Inherited Metabolic Medicine Programme**
- **Mitochondrial Medicine Programme**
- **Pediatric and Developmental Medicine Programme**
- **Sensorineural Pathology Programme**
- **Endocrine Medicine Programme**
- **Hereditary Cancer and Related Syndromes Programme**

Research groups join the different RPs according to the diseases in which they conduct their scientific work and the aspects about such diseases being investigated. The groups are integrated in a programme by means of participating in Lines of Research that are defined on the basis of the programme itself and on the basis of the disease or group of diseases with respect to which the most relevant research in the group in the field of RD is being conducted. Specifically, participation of research groups in RPs is based on the following criteria:

- High scientific level in the disease/diseases in question.
- Proven capacity of interaction and cooperative research between groups. All CIBERER groups working in the field of a specific line of research must participate in said line of research.
- Clear interest in developing translation actions, including clinical trials, and transfer actions.
- Promoting internationalization activities, attending international scientific and clinical forums.

The RPs operate by means of scientific, technical, translational and educational instrumental activities using research support tools.

The RP model is an opportunity for refocusing the research conducted by the research groups and for the groups to cooperate with one another, a higher capability of adapting to translational research needs, and the development of a more dynamic RD research model.

The general characteristics of the 7 Research Programmes, i.e., description of each programme, objectives, the rare diseases studied and the groups forming each of the programmes, is provided below.

Genetic Medicine

Genetic Medicine Programme: consisting of 14 research groups from different fields, including clinical genetics, molecular genetics, molecular and fundamental biology and bioinformatics.

Rare Diseases Studied

- Lafora disease and other rare genetic epilepsies.
- Neuromuscular diseases: muscular dystrophies, spinal muscular atrophy, Charcot-Marie-Tooth neuropathy, Friedreich's ataxia.
- Vascular diseases and diseases of the immune system: disorders affecting the vascular endothelium, causing pathologies such as HHT and complement defects.

Objectives

To incorporate Mendelian or complex diseases affecting an organ or system of the human body, using the hereditary factor as the fundamental criterion for incorporation in the programme.

Specific objectives include: 1) to lead the development of innovations in genomic platforms, 2) to promote translational research in neuromuscular diseases, 3) to offer support for pre-clinical research on rare epilepsies and related diseases, including Lafora disease, and 4) to boost physiopathological study for therapeutic and diagnostic applications in rare vascular pathologies and in complement-mediated pathologies.

Groups forming the RP

Scientific Coordinator: Dr. Guillermo Antiñolo, U702.

- Dr. Eduardo Tizzano Ferrari, U705.
- Dr. Carmelo Bernabéu, U707.
- Dr. Ángel Carracedo, U711.
- Dr. Joaquín Dopazo, U715.
- Dr. Erwin Knecht, U721.
- Dr. Francesc Palau Martínez, U732.
- Dr. Consuelo González Manchón, U734.
- Dr. Santiago Rodríguez de Córdoba, U738.
- Dr. Pascual Sanz, U742.
- Dr. José Serratosa, U744.
- Dr. Javier Díaz Nido, U748.
- Dr. Cecilio Giménez Martín, U751.
- Dr. Margarita López Trascasa, U754.
- Dr. Juan Luque, RP Scientific Manager.

Inherited Metabolic Medicine

Inherited Metabolic Medicine Programme: consisting of 12 research groups from different fields, including clinical genetics, molecular genetics and molecular and cell physiology.

Rare Diseases Studied

- Inherited metabolic diseases: lysosomal diseases, organic acidemias, glycosylation defects, peroxisomal diseases.

Objectives

To study RD having the fundamental aspect of altering homeostasis caused by mutations in genes relating to intermediary metabolism.

The programme specifically seeks to define the genetic cause and the physiopathology of these pathologies affecting biomolecule synthesis, metabolism, transport and storage. They are generally serious diseases involving multiple organs and in many cases reducing the life expectancy and quality of life of patients.

Based on the definition and in depth knowledge about these clinical phenotypes, in addition to evaluating the clinical response to treatments available today, the programme is working on Innovative Therapies, such as the use of chaperones to aid in enzyme functionality.

Groups forming the RP

Scientific Coordinator: Dr. Antonia Ribes, U737.

- Dr. Rafael Artuch, U703.
- Dr. Daniel Grinberg, U720.
- Dr. Virginia Nunes, U730.
- Dr. Manuel Palacín, U731.
- Dr. Vicente Rubio Zamora, U739.
- Dr. Eduardo Salido, U740.
- Dr. Francisca Sánchez Jiménez, U741.
- Dr. Belén Pérez González, U746.
- Dr. Raúl Estévez Povedano, U750.
- Dr. Pilar Giraldo Castellano, U752.
- Dr. Aurora Pujol Onofre, U759.
- Mónica Bescós, RP Scientific Manager.

Mitochondrial Medicine

Mitochondrial Medicine Programme: consisting of 8 research groups from different fields specialized in the study of the physiological and functional aspects of the mitochondrion in different tissues.

Rare Diseases Studied

- Inherited and sporadic encephalomyopathies of mitochondrial DNA (mtDNA) (it would include entities such as KSS, MELAS, MERRF, LHON, NARP/MILS, cardiomyopathies, hearing loss and mitochondrial diabetes, etc.).
- mtDNA maintenance syndromes: depletion syndromes and syndromes with multiple mtDNA deletions, such as MNGIE, PEO, SANDO, S. Alpers, etc.
- Diseases of the OXPHOS system associated with nuclear and assembly genes (alterations of OXPHOS subunits and assembly factors, pathologies affecting mitochondrial transcription and translation, syndromes associated with deficiency of coenzyme q).

Objectives

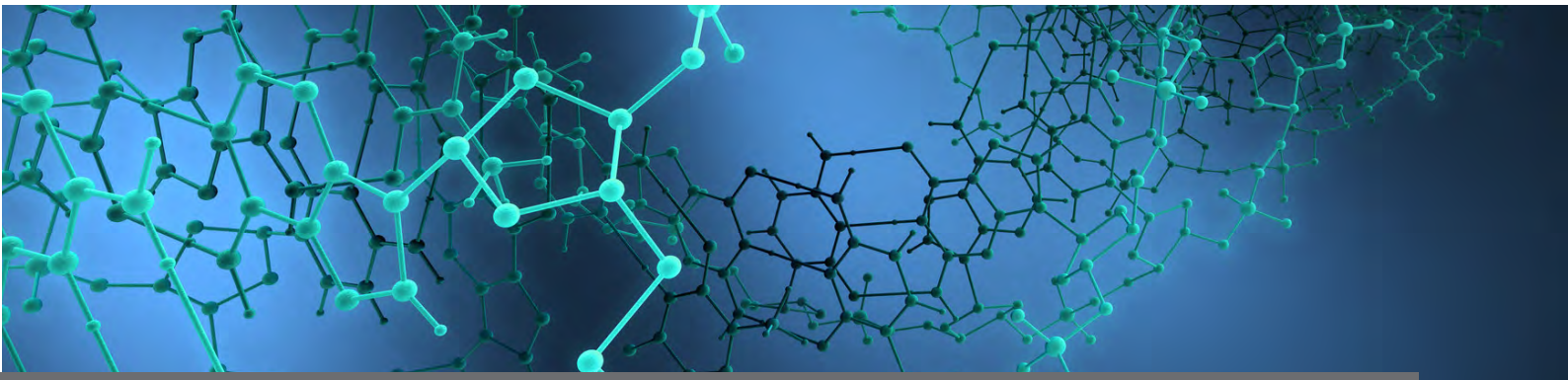
To approach diseases with mitochondria as the physiopathological target affecting an individual's bioenergy balance. It was created independently of the metabolic medicine programme because they involve a significant number of groups with condensed networking work experience that is to be boosted from CIBERER.

The proposed specific objectives are: 1) to study the genome-mitochondrial communication, 2) to study the physiopathology and mechanisms of disease in cellular models and iPSC, and 3) to conduct therapeutic research, ranging from the development of animal models up to the preclinical stage, biomarkers, particularly in neuromuscular pathologies.

Groups forming the RP

Scientific Coordinator: Dr. Miguel Ángel Martín Casanueva, U723.

- Dr. Ramón Martí Seves, U701.
- Dr. José M. Cuezva , U713.
- Dr. Rafael Garesse, U717.
- Dr. Francesc Cardellach, U722.
- Dr. Julio Montoya, U727.
- Dr. Plácido Navas, U729.
- Dr. Jorgina Satrústegui, U743.
- Mónica Bescós, RP Scientific Manager.



Pediatric and Developmental Medicine

Pediatric and Developmental Medicine Programme: consisting of 8 research groups from different fields, including clinical genetics, molecular genetics, molecular biology, cell biology, epidemiology and fetal medicine.

Rare Diseases Studied

- Congenital defects
- Genomic disorders (syndromes caused by genomic rearrangements).
- Disorders of the development associated with learning disability/intellectual impairment.

Objectives

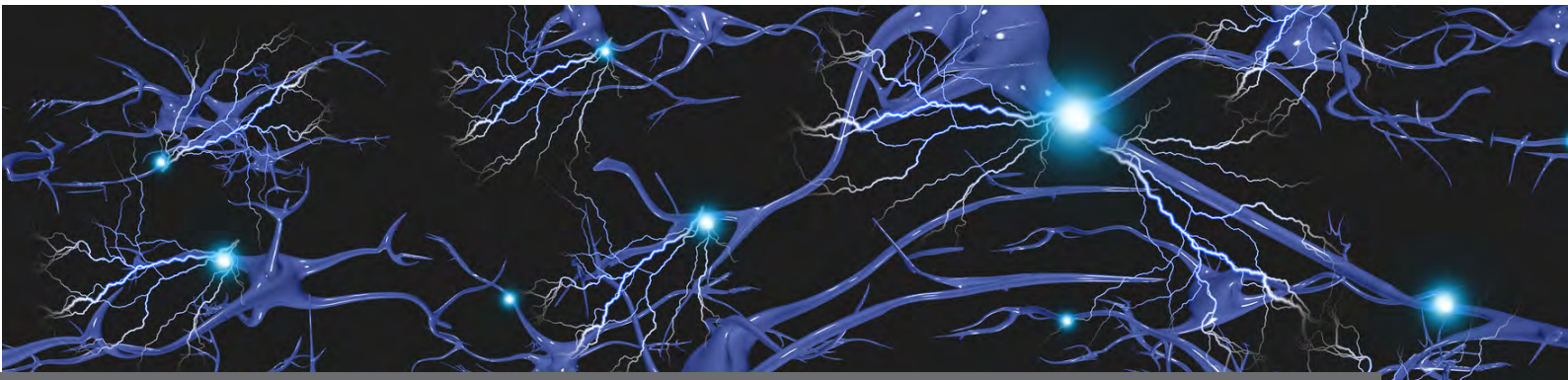
To approach disorders conditioned by anomalous embryonic development, regardless of the cause, involving congenital malformation or a cognitive development disorder, particularly relevant during childhood and during the period of growth and development of the individual.

The specific objectives are: 1) to encourage the development of genomic diagnostic tools for diseases of interest of the RPs, 2) to lead CIBERER research in Innovative Therapies, with a particular emphasis on gene and fetal therapies, 3) to boost clinical research as a result of close collaboration with national hospitals of reference, and 4) to develop tools for epidemiological research in rare diseases.

Groups forming the RP

Scientific Coordinator: Dr. Pablo Lapunzina, U753.

- Dr. Cristina Fillat, U716.
- Dr. Eduard Gratacòs, U719.
- Dr. Mª Luisa Martínez-Frías, U724.
- Dr. Montserrat Milà, U726.
- Dr. Luis Pérez Jurado, U735.
- Dr. Manuel Posada, U758.
- Dr. Víctor Luis Ruiz Pérez, U760.
- Dr. Juan Luque, RP Scientific Manager.



Sensorineural Pathology

Sensorineural Pathology Programme: consisting of 7 research groups from different fields, including clinical and molecular genetics, epidemiology, molecular and cell biology and animal models, for translational purposes by means of implementing new diagnostic algorithms and therapeutic orientation.

Rare Diseases Studied

- Retinal dystrophies
- Isolated and syndromic ocular abnormalities
- Albinism
- Hereditary and congenital hypoacusis

Objectives

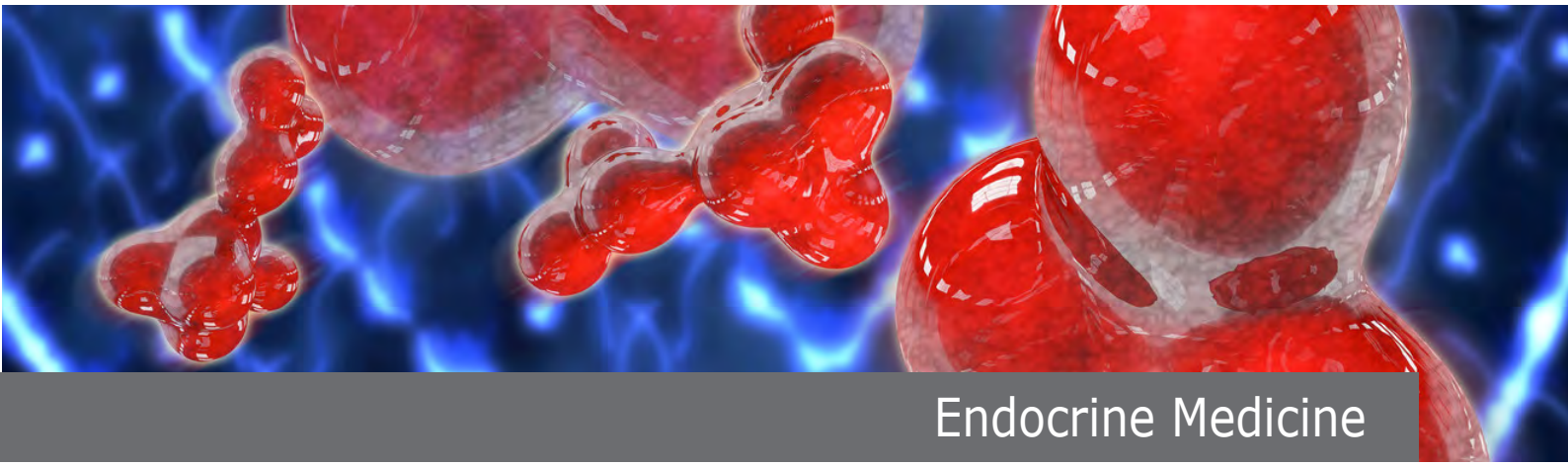
To approach rare diseases having an effect on sensory organs, and particularly on sight and/or hearing.

The strength of the RPs and one of their main objectives is to develop cellular and animal models of RD, particularly for the next period of leading the pre-clinical research on sensorineural RD. In addition, the RPs develop genomic diagnostic tools.

Groups forming the RP

Scientific Coordinator: Dr. Carmen Ayuso, U704

- Dr. Paola Bovolenta, U709.
- Dr. Roser González Duarte, U718.
- Dr. Miguel Ángel Moreno, U728.
- Dr. José María Millán, U755.
- Dr. Lluís Montoliu José, U756.
- Dr. Isabel Varela Nieto, U761.
- Beatriz Gómez, RP Scientific Manager.



Endocrine Medicine

Endocrine Medicine Programme: consisting of 4 research groups from the area of endocrinology and pediatrics, ranging from basic clinical care, study on the molecular basis of a disease and the application of therapeutic solutions.

Rare Diseases Studied

Diseases affecting pituitary hormones and their target tissues, such as:

- Growth hormone (GH): Acromegaly.
- Steroid hormones: Cushing's syndrome, familial glucocorticoid deficiency, androgen deficiency and sexual differentiation anomalies.
- Thyroid hormones: congenital hypothyroidism, Allan-Herndon-Dudley syndrome.

Objectives

To study disorders caused by hormonal dysfunction relating to the pituitary gland and target organs.

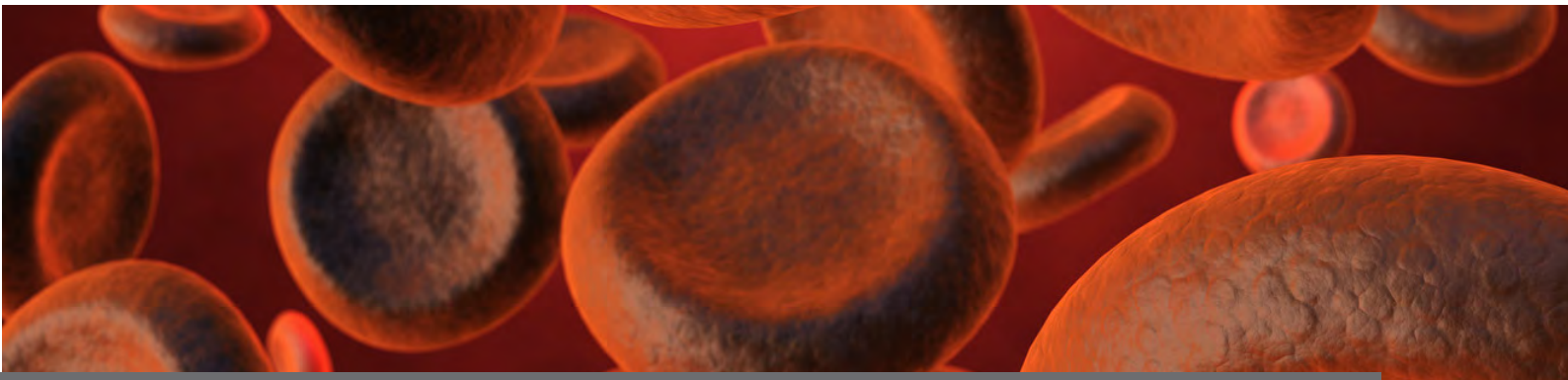
The groups of diseases that stand out:

- Involve growth hormone (GH): Acromegaly and deficiency of GH.
- Involve steroid hormones: Cushing's syndrome, familial glucocorticoid deficiency, androgen deficiency and sexual differentiation anomalies.
- Involve thyroid hormones: congenital hypothyroidism and resistances to thyroid hormones, including the Allan-Herndon-Dudley syndrome.

Groups forming the RP

Scientific Coordinator: Dr. Susan Webb, U747.

- Dr. Juan Bernal, U708.
- Dr. Antonio Carrascosa, U712.
- Dr. Luis Castaño González, U725A.
- Dr. Andrés Medrano, RP Scientific Manager.



Hereditary Cancer and Related Syndromes

Hereditary Cancer and Related Syndromes Programme: consisting of 7 research groups from different fields, including clinical and molecular genetics, regenerative medicine, advanced/innovative therapies, molecular biology and cell biology.

Rare Diseases Studied

- Fanconi anemia and disorders relating to genetic instability.
- Hereditary cancer and pediatric tumors.

Objetives

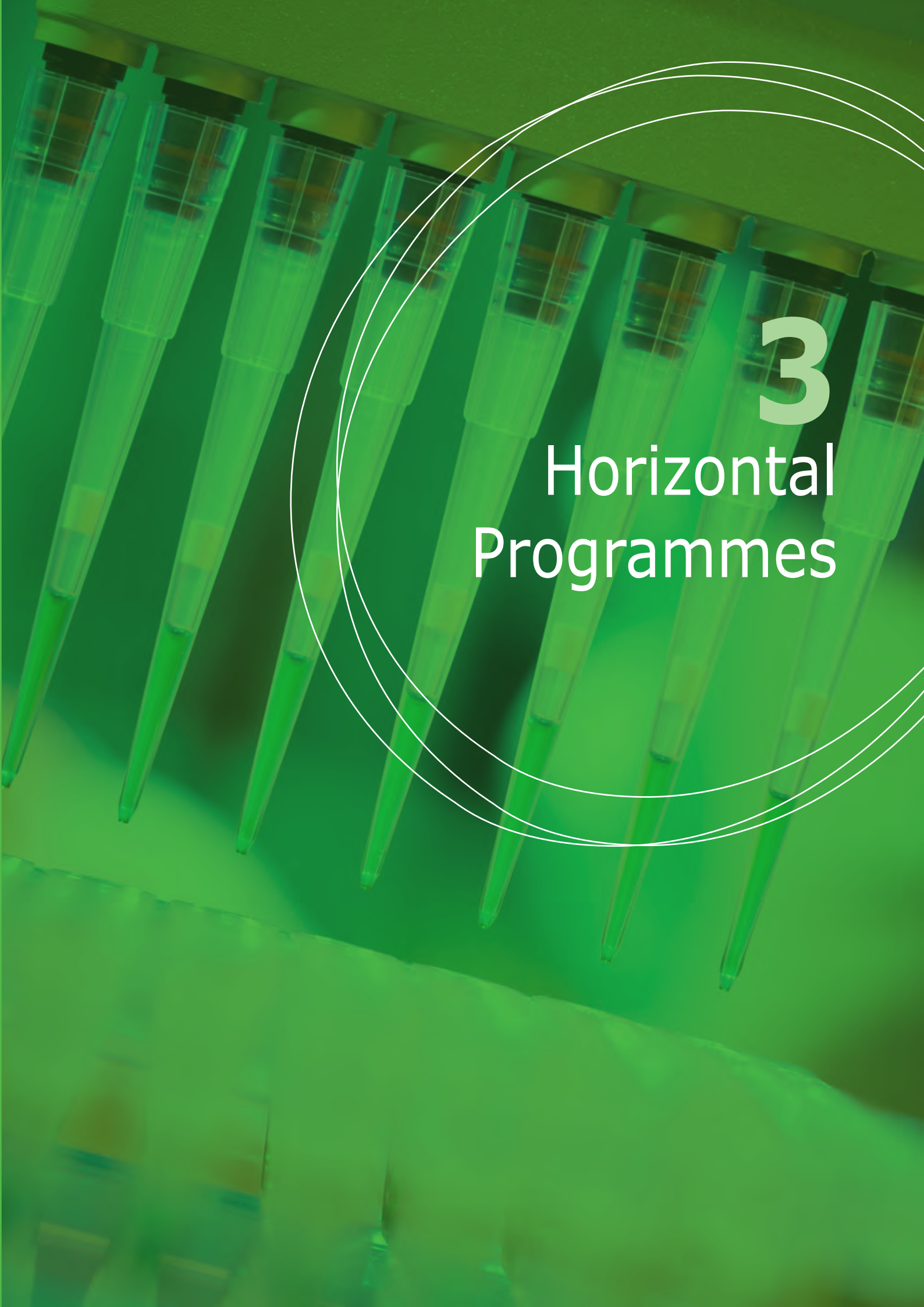
To study the physiopathological mechanisms and genetic basis of hereditary cancer as well as other related syndromes, in which genetic instability is a fundamental component in disease onset or progression.

The specific objectives of this programme focus on the chromosome research, specifically on Fanconi anemia, research on rare tumors, particularly endocrine tumors, and research on advanced therapies (in collaboration with other RPs). Some of the most noteworthy achievements include international clinical trials for gene therapy for Fanconi anemia or the development of tissue cultures for autologous transplant after gene correction for epidermolysis bullosa.

Groups forming the RP

Scientific Coordinator: Dr. Jordi Surrallés, U745.

- Dr. Javier Benítez, U706.
- Dr. Juan A. Bueren, U710.
- Dr. Marcela del Río, U714.
- Dr. Federico Pallardó, U733.
- Dr. José Fernández Piqueras, U749.
- Dr. Rosario Perona, U757.
- Dr. Andrés Medrano, RP Scientific Manager.



3 Horizontal Programmes

Human Resources Programme

Description

CIBERER designs and executes the start-up strategy for a series of actions intended for providing the different research groups with a critical mass of scientific and technical staff. These hiring actions have integrated new research staff into the groups of the different institutions forming CIBERER. The policy implemented by CIBERER ever since it was founded has resulted in reinforcing the research groups, consisting of personnel attached to CIBERER that comes from the same groups forming part of the Consortium Institutions and of CIBERER staff. As a result of this reinforcement of the critical mass, advancements in RD research could be consolidated.

CIBERER employees are reassigned to the groups considering needs assessment and compliance with the objectives and strategic lines of the Center. All the information obtained through the different activity evaluation and follow-up processes conducted for the CIBERER groups and hires helps them to develop new RPs.

Human talent is a fundamental component for implementing staff policy. Managing this talent is the key to CIBERER's success, so the primary objective of Human Resources is to appropriately consider employee training requirements.

Objetives

For CIBERER, the key to success is based on the research potential, staff professionalism and commitment to RD. For this reason, for the second period 2010-2013, the objectives of the Human resources programme are for the purpose of reinforcing research excellence of the CIBERER staff and the high level of the specialization of hires in RD. To meet these objectives, for 2013 CIBERER set the following goals:

- To give added value to CIBERER staff.
- To draw up a follow-up model to track the staff's scientific activity in RD.
- To establish company policies for scientific and technical CIBERER staff for the purpose of:
  - developing a corporate culture.
  - boosting, developing and augmenting the skills of the hires in the field of RD.

Resources Used

Economic resources: The CIBERER HR Programme has historically been the programme that absorbs the largest amount of economic resources for funding it. It involves the 59 research groups from the Consortium with the sole exception of the affiliated group (U725A) which, by definition, cannot obtain funding to hire staff.

The funds assigned to the programme were primarily intended to fund hired staff wages. These funds are distributed among the different items of the Research Programmes, Instrument Platforms and the Management Office. However, other types of expenses are also covered in the programme, such as those resulting from occupational health and safety and from health monitoring, the insurance directly linked with the hired staff (civil liability and accident insurance), or the running costs in the acquisition of material for the job for hires.

Staff resources: CIBERER hires, CIBERER grant holders.

Services: Management Office – HR Department.

Results

CIBERER research activity means that each of the hires is assigned to one of the Research Programmes or platforms of the Center. CIBERER brought together over 700 investigators in 2013, including personnel attached to CIBERER, grant holders and hired staff with an average age of 35 years, showing a clear commitment to young investigators.

Diversity is an added value, because the processes to be performed can be approached from different angles. In this regard, in 2013 88% of CIBERER professional employees held a bachelor's degree, 50% of all employees held a PhD, came from over 10 different nations. Furthermore, 75% of the staff was comprised by women.

The research and technical staff hired by the entity amounted to 157 employees in all of 2013, with the following professional category:

CATEGORY	Nº. OF EMPLOYEES
PHDs > 3 YEARS	58
PHDs < 3 YEARS	19
BACHELOR DEGREES	58
ASSOCIATE DEGREES	1
VOCATIONAL TRAINING	17
TOTAL	153

Training Programme

Description

The Transverse Instrument Platform (PITER) or training programme in rare diseases is the instrument by means of which CIBERER promotes and supports training its investigators, in addition to supporting the initiative the research groups follow.

The training offer consisted of:

- CIBERER predoctoral aid: specific tool for attracting recent university graduates to CIBERER groups, allowing remuneration for work immediately after joining without having to wait until the general calls for proposals for predoctoral aid are resolved.
- Aid for Mobility: aid so that CIBERER investigators can hold internships for up to three months in other internal or external research groups.
- Courses: aid for internal CIBERER courses and for funding the attendance of members of the CIBERER groups to courses of specific interest for some of the strategic lines of the Center.

Objetives

The objectives of the Training Programme are:

- To favor incorporating research staff in training to the CIBERER groups.
- To directly organize or help organize training courses and activities.
- To promote mutual knowledge and collaboration between CIBERER groups.
- To collaborate in the internal dissemination of the CIBERER research activity.

Recursos empleados

Staff resources: Training Manager, who works part-time in organizing and controlling the CIBERER training activities. CIBERER staff of the Predoctoral Aid Programme.

Services: Management Office – Training Department.

Results

The following can be mentioned as the 2013 Training programme activity results:

Call for proposals for Predoctoral Aid:

After concluding the agreement with Bancaja Foundation, the 2013 call for proposals for predoctoral aid was taken on in its entirety with CIBERER funds. This call for proposals allowed incorporating eight young graduates so they could do their predoctoral work. The intention for 2013 was to split the call for proposals into two periods and announce the remaining aid, for up to 20 people in total, in a new call for proposals in June 2013. Ultimately this could not be done given the general limitations on hiring and incorporating staff in public administrations, which affected this call for proposals.

The results of the 2013 Call for Proposals for Predoctoral Aid, indicating the name of the awarded candidates, the Consortium Research Center where they will be working, and the project they joined, are presented below.

Name and Last Names	Group and Associated Project
Sara Morón López	CIBERER Group 705. Translational research in Spinal Muscular Atrophy: Phenotype modifiers, motor neuron models based on iPSCs and neuromuscular development pathology.
Rocío Martínez Regueiro	CIBERER Group 711. SCA36: Molecular dynamics, phenotype and bioinformatic tools.
Rosa D. Hernansáiz Ballesteros	Group 715. New genes and mechanisms in retinal dystrophies. Application of whole exome sequencing and systems biology, functional studies in an animal model and clinical characterization.
Francisco Zurita Díaz	Group 717. Use of induced pluripotent stem (iPS) cells for the study and treatment of mitochondrial diseases.
María Baño Padín	Group 722. Mitochondrial involvement in restricted intrauterine growth and the associated cardiovascular remodeling.
Sandra Jiménez Gancedo	Group 729. Phenotypic and molecular characterization of coenzyme q deficiency syndrome.
Laura Amarilis Indriago Acha	Group 732. Dissection of the mitochondrial physiopathology of Charcot-Marie-Tooth neuropathy.
Fernando Corvillo Rodríguez	Group 754. Complement system involvements in human pathology.

The information relating to the grants awarded for the 2013 call for proposals and to the follow-up and closure of the 2012 call for proposals shows that the objectives were met with a high degree of compliance:

- Percentage of withdrawals before the year of validity of the grant concluded, continuing to work in the group. There was only one withdrawal before the end of the validity period. This follows the trend established in 2010 and 2011, where there was only an 11% withdrawal rate, in contrast with previous years: 60% (9 out of 15) in 2007 and 43% (10 out of 23) in 2008. The reason for this is associated with external factors, such as the fact that the delay in setting the dates for deciding who will be awarded the general grants in the calls for proposals is increasingly greater.
- Number of grants in the 2013 call for proposals: 8 grants. Within the range established as optimal (8 to 12).
- Average grade of the candidates in the 2013 call for proposals: 2.56. Three tenths lower than the average grade in the 2012 call for proposals, but considerable higher than the cutoff point of 2.2.

Aids for Mobility

In 2013, aids for mobility opened up to external, national and international mobility, eliminating the restriction from 2012 that limited these aids to intramural mobility. Several investigators could therefore benefit from this programme to expand their training and advance the projects in which they were involved.

- Number of examples of mobility: 18 requests, consolidating the trend established in previous years

  (2007=1; 2008=7; 2009=8; 2010=11; 2011=10; 2012=13; 2013=18).

  Fifteen candidates were awarded aids for mobility, because 3 of the requests for aid for mobility were for mobility within the same province, which cannot receive economic aid.

One way to estimate the efficiency of internships is the feedback received in a questionnaire that the recipients are asked to complete after completing their internship. They are specifically asked to answer five different questions, giving an answer on a scale of 1 to 5, 1 being the worst and 5 being the best rating. Average results for the different parameters in 2013 are shown below:

- General interest in the mobility: 4.5
- Usefulness for my current research work: 4.5
- Future applicability of the knowledge acquired: 4.5
- Collaboration offered by the receiving group: 5
- Aid for mobility management: 5

La siguiente tabla recoge las movilidades realizadas en 2013:

MOBILITY BETWEEN PROVINCES		
Name	**Source group**	**Receiving group**
Mª Isabel Álvarez	726	711
Ivon Cusco Martí	735	715
Marta de Castro	718	715
Inés García	723	732
Begoña Díez	710	VSSR University Medical School, Milán (Italy)
Florentina Sava	718	University of Oklahoma, Oklahoma City, (USA)
Almudena Pino	741	Technische Universität, Dresden (Germany)
Beatriz Morte	708	715
Celia Medrano	746	Center of Human Genetics, Leuven (Belgium)
Rocío Martínez	711	704
Lidia Carreño	701	723
Adelaida Celaya	761	733
Sara Pérez-Luz	748	732
Beatriz Morte	708	715
Bárbara Torrico	720	Universitetet I, Bergen (Norway)
MOBILITY IN THE SAME PROVINCE		
Name	**Source group**	**Receiving group**
Marta Seco	733	721
Jair Tenorio	760	753
Marta Seco	733	742

Aids for the attending and/or organizing courses

CIBERER directly organized two specific training courses on its own:

- "Introduction to the analysis of phenotypic and functional networks in rare diseases". Universidad de Málaga. June 13 and 14, 2013.
- "Animal Model Phenotyping". Escuela de Medicina Veterinaria, UCM. December 9-13, 2013.

For these two courses, aids for attended were granted to members of CIBERER groups. A total of 26 aid packages were offered to cover total expenses for attending recipients.

Furthermore, three additional calls for proposals for aid for attending external courses of special interest for the work of its own investigators were opened. A total of 8 aid packages were offered for attending the following activities:

- "15th International Symposium on Purine and Pyrimidine Metabolism in Man". Hotel Velázquez, Madrid. June 9-13, 2013.
- "Clinical practice guidelines on rare diseases". Institute Superiore di Sanità, Rome, Italy. July 8-12, 2013.
- "Inner Ear Biology Workshop 2013. Universidad de Alcalá de Henares, Madrid. September 10-13, 2013.

Organization of the Annual CIBERER Meeting

The 6th Annual CIBERER Meeting took place in Euroforum del Escorial in Madrid from February 28 until March 1. 185 people attended this plenary meeting, and most of the attendees were investigators from CIBERER groups. For a networking Center like CIBERER, the Annual Meeting is a unique opportunity to meet with investigators, to learn about the latest advancements and to debate new actions.

The meeting served as a forum for presenting and debating the advancements made by the different lines of research of the CIBERER groups. It reflects the actions of the seven CIBERER research programmes, in addition to the activities of their scientific activity support programmes and platforms. The participation of investigators undergoing training was paramount, and the junior affiliated investigators and hires present at the meeting played an important role.

The programme also presented the actions of the different CIBERER platforms and the sharing of short- and mid-term objectives and strategy.

Research Project Programme: Intramural Actions (ACCI) and External Projects

Cooperative and Complementary Intramural Actions (ACCI)

To encourage the development of cooperative research projects on a Rare Disease (RD) or group of related RD, a call for proposals for Cooperative and Complementary Intramural Actions was launched in 2012. Ten top-quality proposals were approved. The following table shows data about all the projects that were co-funded with CIBERER funds and active during 2013.

TITLE	PI	COORD. UNIT	PARTICIPATING UNITS
Physiopathological Basis of Lafora Disease	Dr. Sanz	U742	U709, U721, U733, U738, U744
Identification of new physiopathological mechanisms in Kindler Syndrome	Dr. del Río	U714	U726, U733
Preclinical study of gene therapy for MNGIE by means of ex vivo transduction of the TYMP gene using a lentiviral vector in a mouse model with humanized skin.	Dr. Martí	U701	U714, U722
Study of the putative role in breast cancer susceptibility of a new Fanconi Anemia gene. A massive genetics and functional analysis.	Dr. Benítez	U706	U749, U745 (sin presupuesto)
Use of induced pluripotent stem (iPS) cells for the study and treatment of mitochondrial diseases.	Dr. Garesse	U717	U729, U746
New genes and mechanisms in Retinal dystrophies. Application of whole exome sequencing and systems biology, functional studies in an animal model and clinical characterization.	Dr. Ayuso	U704	U702, U715, U755
Identification of genetic variants modifying the phenotype of Leber's optic atrophy and mitochondrial non-syndromic sensorineural hearing loss with homoplasmic mutations of mitochondrial DNA.	Dr. Martín Casanueva	U723	U701, U727
Genetic diagnosis and possible treatments of albinism.	Dr. Montoliu	U756	U711
Identifying and characterizing new genes responsible for osteogenesis imperfecta.	Dr. Ruiz Pérez	U760	U753
Identification of patients with mutations in genes involved in the biosynthesis and transport of mitochondrial energy metabolism co-factors.	Dr. Ribes	U737	U703, U746

External Projects

Research of excellence requires top-level economic, material and human resources to develop the activities and comply with objectives. Drawing in competitive and non-competitive resources is fundamental for developing far-reaching projects and actions in RD.

In 2013, the CIBERER Management Office and the groups involved in the different actions continued working in that sense. The main actions in 2013 can be accounted for as:

Aids granted in 2013

The following table shows the grants and aids that were given in 2013 to competitive CIBERER projects or actions either by public institutions or private institutions. The type of project, the name of the principal investigator, the title or reason for the action and the entity granting the aid are provided.

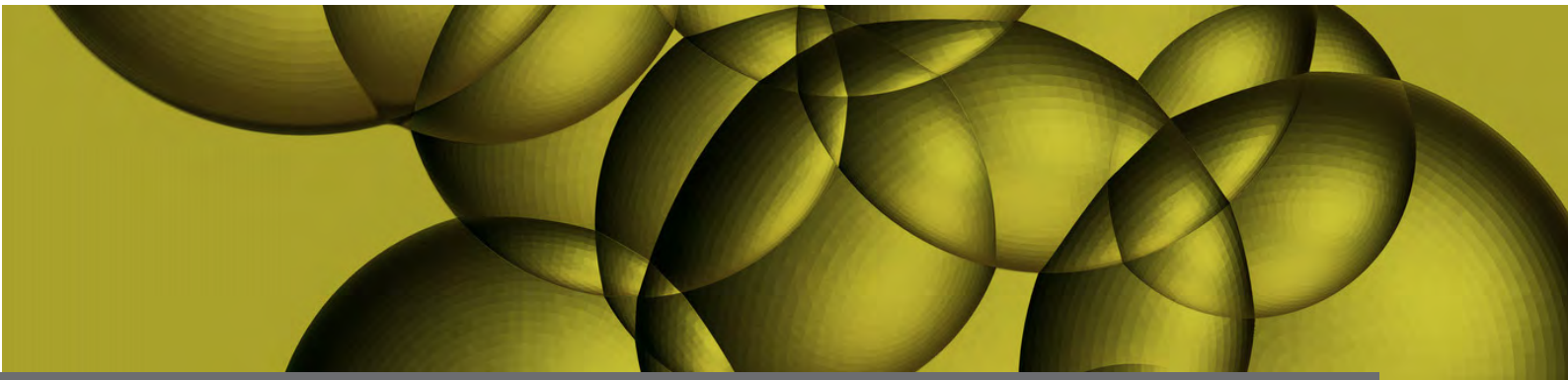
PROJECTS GRANTED IN 2013 IN COMPETITIVE CALLS FOR PROPOSALS			
Group	**Project PI/ Work Group**	**Title**	**Funding Agency-Programme**
International Scope			
CIBERER (U746, U720, U737, U703)	Dr. Couce	European Network and Registry for Homocystinurias and Methylation Defects (E-HOD).	DG SANCO–Project
CIBERER U750	Dr. Estévez	CLC chloride channels and Megalencephalic leukoencephalopathy: molecular mechanisms and therapeutics.	CIBERER-E-RARE 2
CIBERER U708	Dr. Bernal	THYRONERVE	CIBERER-E-RARE 2
National Scope, Public Entity calling for Proposals			
CIBERER U735	Dr. Cuscó	Study of the pathways involved in the autism spectrum: Functional consequences of genetic and epigenetic variants	ISCIII – FIS Health Research Projects
CIBERER U701	Dr. Pinòs	Advancements in McArdle's disease. New therapeutic approaches and development of a new, non-invasive diagnostic method in patients.	ISCIII – FIS Health Research Projects
Private Entity Calling for Proposals			
CIBERER U759	Dr. Pujol	Cellular and molecular characterization of the relationship between oxidative stress and inflammation in adrenoleukodystrophy: therapeutic implications	Mehuer Foundation
CIBERER U708	Dr. Morte	Preclinical study of the effectiveness of TRIAC, a thyroid hormone analogue, in the treatment of Allan-Herndon-Dudley Syndrome.	Mehuer Foundation

Aids in force in 2013

21 projects or events that had been receiving a grant or aid since 2009 were carried out in 2013 and they were managed by CIBERER. The following table shows the type of project, the group and the name of the principal investigator, the title or reason for the funded event and the entity granting the aid, ordered by year of grant.

PROJECTS GRANTED IN COMPETITIVE CALLS FOR PROPOSALS THAT ARE ACTIVE IN 2013				
Group	**Project PI/ Work Group**	**Title**	**Funding Agency**	**Period**
International Scope				
CIBERER	Dr. Palau	Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) (CIBERER participa como miembro asociado).	7PM. CAPACITIES	2009-2013
CIBERER	Dr. Palau	RD PORTAL 3 ORPHANET.	DG SANCO – Joint Action	2010-2013
CIBERER	Dr. Palau	EUCERD JOINT ACTION.	DG SANCO – Joint Action	2012-2015
CIBERER	Dr. Palau	RD-Connect. An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research.	7PM. HEALTH	2012-2016
CIBERER (U746, U739, U737, U703)	Dr. Ugarte	E-IMD. European registry and network for Intoxication type Metabolic Diseases.	DG SANCO – Project	2011-2014
CIBERER	Miquel Calvet	CommHERE -Communication of European Health Research (CIBERER participa como tercera parte del ISCIII).	7PM. HEALTH	2011-2013
National Scope, Public Entity Calling for Proposals				
CIBERER U732	Dr. Espinós	Miguel Servet Contract, Dr. Carmen Espinós (U732). Associated PROJECT: "Genetic and Disease Mechanisms in Inherited Neuropathies".	ISCIII – FIS Subprogramme HR -Miguel Servet	2008-2014
CIBERER U732	Dr. Espinós	Translational research and disease mechanisms in inherited peripheral neuropathies.	ISCIII – FIS Research projects in health	2013-2015
CIBERER	Management Office	Contract for Transfer Support Technician: Andrés Medrano.	MICINN- PTA Subprogramme	2010-2013
CIBERER	Management Office	Contract for Transfer Support Technician: Mª Elena Mateo.	MICINN- PTA Subprogramme	2010-2013
CIBERER U753	Dr. Martínez-González	Genomic, epigenetic and transcriptional study of tumors in polymalformative genetic syndromes.	MICINN-Non-oriented, Fundamental Research Project Subprogramme	2011-2014
CIBERER U722	Dr. Garrabou	Mitochondrial alterations in cellular models of Parkinson's disease (LRRK2 and Parkin): Therapeutic potential of mitochondrial function modulators.	ISCIII – FIS Health Research Projects	2012-2014

PROJECTS GRANTED IN COMPETITIVE CALLS FOR PROPOSALS THAT ARE ACTIVE IN 2013				
Group	**Project PI/ Work Group**	**Title**	**Funding Agency**	**Period**
CIBERER U732	Dr. González Cabo	Axonal physiopathology of Friedreich's ataxia: Axonal transport and degeneration.	ISCIII – FIS Health Research Projects	2012-2014
CIBERER U732, U733, U713, U743, U755	Dr. Palau	Translational Research, Experimental Medicine and Therapeutics on Charcot-Marie-Tooth Disease	ISCIII-IRDiRC	2012-2016
Private Entity Calling for Proposals				
CIBERER U732	Dr. Palau	Integrated Research Consortium for Friedreich's ataxia: physiopathological and therapeutic approach (FAIR).	Fundaciò Maratò TV3	2010-2014
CIBERER U742	Dr. Sanz	Lafora progressive myoclonus epilepsy: Physiopathological basis of the disease and therapeutic approaches.	Fundaciò Maratò TV3	2010-2013
CIBERER U710	Dr. Bueren	Regenerative medicine for Fanconi anemia: generation of disease-free patient-specific iPS cells, derived hematopoietic progenitors and platelets.	Fundaciò Maratò TV3	2013-2015
CIBERER U732	Dr. González Cabo	Identification of biomarkers associated with Friedreich's ataxia	Ayudas a la investigación de la Fundación Alicia Koplowitz	2011-2013
CIBERER U735	Dr. Cuscó	Generation of iPSC cells to study neurodevelopmental disorders: Autism and Williams Syndrome.	Fundación Ramón Areces	2012-2014
CIBERER U708	Dr. Morte	Allan-Herndon-Dudley Syndrome: Molecular mechanisms and therapeutic approaches in the model of the disease.	Fundación Ramón Areces	2012-2014
CIBERER U708	Dr. Morte	Molecular dissection of human deficiencies in the intracellular transport of thyroid hormones.	SENDIMAD	2012-2013



Translation Programme

Description

The process of transferring basic science knowledge to the search for effective therapeutic or preventive interventions requires non-stop interaction, a deliberate exchange of resources and knowledge, to make sure that basic science discoveries benefit patients. The objective is to efficiently apply the knowledge of cellular, molecular, physiological, chemical or genetic processes to the search for effective treatments or for prevention or diagnostic techniques, approaching the work from bench to bed-side.

A fundamental agent in the CIBERER science and technology system for group activity is the National Health System (NHS) as a coordinated set of health services offered by the Public Administration and Autonomous Communities.

CIBERER is responsible for leading the research that is being carried out in the organization into clinical practice so that it directly and effectively benefits society and the National Health System.

In this regard, relations with the health sector and specifically with the National Health System (NHS) are the best way to implement the social return of research. Our research groups, many of which are integrated in the hospital and healthcare field, seek to develop knowledge that can be applied as clinical solutions.

Objetives

The general objective is to promote top-quality translational research, translating the results of basic, clinical, epidemiological, health services and public health research to the National Health System (NHS), the Spanish System of Science and Technology, to patients and to society as a whole.

Resources used

Staff resources: Translation Manager with the support of the team of Scientific Activity Managers.

CIBERER groups are involved in the different links of the value chain, ranging from developing basic knowledge to applying it in routine clinical practice. That potential of complementary profiles must be put to use to favor translation by means of networking.

Services: Management Office.

Results

Existing collaborations and establishing new collaborations with Linked Clinical Groups (LCG) in the framework of the NHS

As established in Article 12(k) of the CIBERER Statutes, the Scientific Director is responsible for presenting and reporting to the Permanent Commission proposed scientific agreements and association agreements before signing them. Furthermore, as established in Article 28 of the Consortium Statutes, subject to the Scientific Director's report and a favorable report from the Permanent Commission, the Governing Board may associate NHS centre clinical groups with CIBERER. This association would be necessary to carry out CIBERER programmes by means of specific agreements.

Therefore, in the framework of its Strategic Plans in 2013, CIBERER opened up the possibility of including new Linked Clinical Groups resulting from the change in the Statutes in 2010, thereby offering a chance to conduct translational research having an even greater reach.

This will allow CIBERER groups to collaborate with groups that have vast clinical experience with RD, accelerating the final translation of the research conducted by CIBERER groups into the NHS.

In summary, efforts are pooled within the framework of skills and expertise that are characteristic of each of them, health centres and CIBERER research groups, developing cooperative, multidisciplinary and translational research activities, as well as working to transfer research and development results and handling scientific training specialized in Biomedicine, and specifically in the area of rare diseases.

From a strategic viewpoint, this process was started by the Clinical groups who had been collaborating with CIBERER research groups and belonged to the Pediatric and Developmental Medicine Research Programme coordinated by Dr. Pablo Lapunzina.

After selecting and validating the proposed LCG according to the criteria established by the ISCIII during the 2011-2012 period, and as declared during the 6th CIBERER Annual Meeting in February 2013, the association of four clinical groups with vast clinical experience that would greatly complement the lack of dysmorphologists in the field of the CIBERER was proposed by the Pediatric and Developmental Medicine Research Programme for approval by the CIBER-Rare Diseases Steering Committee.

The LCG are the following:

- Dr. Isabel Tejada (Hospital Universitario Cruces, Bilbao).
- Dr. Jordi Rosell (Hospital Universitario Son Espases, Palma de Mallorca).
- Dr. Feliciano J. Ramos (Hospital Universitario Lozano Blesa, Zaragoza).
- Dr. Encarnación Guillén (Hospital Universitario Virgen de la Arrixaca, Murcia).

Following a similar process, at the end of 2013 the Inherited Metabolic Medicine Programme initiated proceedings to link clinical groups, and the agreements will be signed at some point in 2014.

Furthermore, clinical groups will continue to be associated with other CIBERER Research Programmes to the extent possible.

Support for preparing Clinical Practice Guidelines, Protocols and Informative Material for Patients

The numerous CIBERER research groups work to develop products that are clearly useful in clinical practice in relation to RD, such as clinical guidelines, operating protocols and informative material for patients.

The fundamental objectives of drawing up CPGs (and protocols) are: to reduce variability in the use of resources, to reduce uncertainty in clinical practice and to develop healthcare quality standards.

The objective of drawing up informative material for patients and their families is to provide reliable information about RD for patients, taking into consideration most recent scientific evidence, expert recommendations and patient needs. This information must consist of relevant content and quality for patients, and especially be adapted to the level of understanding of patients.

Particularly noteworthy in the field of Clinical Practice Guidelines is the work being done by Work Group on Cancer in Polymalformative Genetic Syndromes (gT-CSgP) with the participation of several CIBERER units, coordinated by Dr. Víctor Martínez-González, a CIBERER employee. As described by the coordinator himself, the objective of this group is to offer biohealthcare professionals up-to-date information about the clinical and molecular aspects of syndromes of this type and their associated neoplasias to serve as a leader in diagnosis, prevention and follow-up with patients and family members, an in teaching and research. To that end, the GT-CSGP tries to cover this void by establishing various approach strategies from a broad multidisciplinary perspective.

In 2013, CIBERER compiled Clinical Guidelines, Reports and Opinions of said Reports through its database accessible to the research groups over the Intranet. Some of these documents were published on the web page and in monthly CIBERER newsletters.

CIBERER was also actively involved in drawing up a number of Clinical Guidelines and informative material for patients, such as:

- Title: **"Androgen Insensitivity"**

  Summary: Macrocephaly-Capillary Malformation (M-CM) Syndrome is a complex development disorder characterized by macrocephaly, capillary malformations, overgrowth/asymmetries and neuroimaging abnormalities. The guideline includes diagnosis and follow-up protocols, the minimum information necessary about a M-CM Syndrome patient, as well as a patient information sheet.

  Authors: Dr. Víctor Martínez-González and Dr. Pablo Lapunzina (U753) Work Group on Cancer in Polymalformative Genetic Syndromes. Work Group Coordinator: Dr. Víctor Martínez-González (U753).

  http://gtcsgp.files.wordpress.com/2012/02/gt-csgp-m-mc.pdf

- Title: **"Clinical Guideline for Aniridia, Wilms' Tumor and Wagr Syndrome"**

  Authors: Dr. Isabel Lorda-Sánchez, Dr. Eddy Rene González Flores and Dr. Carmen Ayuso (U704). Work Group Coordinator: Dr. Víctor Martínez-González (U753).

  http://www.ciberer.es/documentos/guias/CSGP-WAGR.pdf

- Title: **"Guideline for Multiple Endocrine Neoplasia type 1 (MEN 1) Patients and Family Members"**

  Summary: Informative brochure for patients and family members summarizing multiple endocrine neoplasia type 1 (MEN 1), symptomatology and therapeutic possibilities.

  Authors: Sociedad Española de Endocrinología y Nutrición (Spanish Society for Endocrinology and Nutrition). CIBERER. IPSEN.

  http://www.seen.es/docs/publico/enfermedades/otras/FolletoMen1_2.pdf

- Title: **"I want to know what HHT is"**

  Summary: Informative brochure for patients and family members explaining Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu Osler Weber disease, clinical manifestations, genetics, diagnosis, treatment, pregnancy and HHT, pediatrics and HHT and centres with experience in HHT.

  Authors: Dr. Carmelo Bernabeu and Dr. Mª Luisa Botella (U707).

  http://www.ciberer.es/documentos/guias/Triptico%20Unidad%20HHT.pdf

CIBERER Clinical Guidelines are regularly added to the CIBERER database (in the "documentación" section on the CIBERER web page or directly at http://www.ciberer.es/index.php?option=com_docman&task=cat_view&gid=41&Itemid=194), which helps disseminate the information to the remaining CIBERER groups, healthcare professionals and the general public.

Support for the development of therapeutic solutions: clinical trials, advanced therapies and orphan drug designation

In keeping with its strategic objectives, CIBERER facilitates and encourages its research groups to participate in national and international trials, aimed at the development and validation of therapies for RD.

In 2013, CIBERER started to more actively boost research projects in advanced therapies (gene therapy, cell therapy and tissue engineering), preclinical research projects and research on the biology of stem cells, particularly iPS cells, to allow future personalized cell therapy and regenerative medicine developments. This can be seen both in the granted ACCI (gene therapy for MNGIE and cell therapy for mitochondrial diseases), and in other externally funded CIBERER projects (Fanconi anemia and Autism/Williams Syndrome), and by means of organizing the Conference on «Advanced therapies for the treatment of Rare Diseases», on October 25 in the Palacio Municipal de Congresos in Madrid.

Furthermore, CIBERER acts as an advisor and driving force in any initiative relating to orphan drug designation that may arise from its research groups. This orphan drug designation is necessary for being eligible for the 2020 Horizontal Programme aid for the start-up of clinical trials on RD. CIBERER is a sponsor of the orphan drug "Lentiviral vector containing the Fanconi anemia A gene (FANCA)" for the treatment of this disease, developed and validated by Dr. Juan Bueren, Head of CIEMAT Group U710.

Participation in the "EUCErD Joint action: Working for Rare Diseases"

The EUCERD Joint Action: Working for Rare Diseases (http://www.eucerd.eu/?page_id=284) has been created to offer support to the European Union Committee of Experts on Rare Diseases (EUCERD), in aspects holding specific interest for the committee that improve knowledge about Rare Diseases in the European framework. This Joint Action, which commenced on March 1, 2012 and will support EUCERD activities for 3 years, is funded by the Executive Agency for Health and Consumers (EAHC) and led by Professor Kate Bushby, Vice-President of this committee of experts.

The CIBERER participates in this project as a partner and coordinator of work package 7 (WP7) on the Quality of Life and Expert Centres in close collaboration with the Ministry of Health, Social Services and Equality. The main task in this WP is to identify those actions that allow improving access to better quality medical assistance, covering the entire spectrum of services, from diagnosis, healthcare and rehabilitation, to the efficient improvement of the quality of life of the people with Rare Diseases (RD).

In 2013, CIBERER continued working on this important European translational field activity, studying various initiatives of the Member States that seek to improve the quality of life in the people suffering from a rare disease. Work this year focused on the identification of good practices existing in Member State health systems, with a special emphasis on those activities located in centres of expertise. The factors affecting the decisions on policies relating to the quality of care in RD, as well as the internal organization of the health systems will also be analyzed so that they can be adapted to policies and to patients with RD.

Maintenance of healthcare translation collaboration agreements, including patient registries for clinical research

The CIBERER has been entering collaboration agreements with a number of entities, many of which work in the translational field, for some time.

The most noteworthy of such agreements are the general agreements entered into with the Spanish Federation of Rare Diseases (FEDER), Public Andalusian Progress Foundation or the Medina Foundation, setting up stable channels for collaboration offering consistence and continuity to any initiatives, programmes, projects and actions aimed at the group of people with rare diseases that may be developed jointly by both Institutions.

The importance of registries in the field of rare diseases must be highlighted within the field of translational research.

Little documented information about the epidemiology of rare diseases makes it obvious that there is a need to estimate the total number of people affected and the prevalence of each disease, and to evaluate the natural history of rare diseases for the purpose of adapting healthcare to it and being able to improve disease follow-up.

Therefore, in 2013 CIBERER continued working on the start-up and maintenance of various registries, such as:

- Launch and maintenance of the **Rare Disease Registry** of the Rare Disease Research Institute (IIER-ISCIII), coordinator: Dr. Posada (U758). Result of an Intramural project that started in 2009, with the participation of other CIBERER groups: U711 (Dr. Carracedo), U714 (Dr. del Río), U747 (Dr. Webb), U752 (Dr. Giraldo) and U754 (Dr. López-Trascasa).
- Maintenance of the **Fanconi anemia Database**, coordinators: Dr. Surrallés (U745) and Dr. Bueren (U710), (together with the National Oncological Research Centre-CNIO Foundation and the Environmental and Technological Research Centre-CIEMAT).
- **E-IMD European registry and network for Intoxication type Metabolic Diseases.** E-IMD is an on-going project of DG-SANCO to create a metabolic rare disease online registry. Led by Dr. Ugarte (U746) with the participation of Dr. Artuch (U703), Dr. Ribes (U737) and Dr. Rubio (U739).
- **E-HOD European network and registry for homocystinurias and methylation defects (E-HOD)**. E-HOD is an on-going project of DG-SANCO to create an online registry of **homocystinuria** and other diseases caused by methylation defects. Led by Dr. Couce (U737) with the participation of Dr. Artuch (U703), Dr. Grinberg (U720) and Dr. Pérez (U746).
- **European Registry of Wolfram, Alström and Bardet-Biedl and other Rare Diabetes Syndromes**, a project funded by the DG-SANCO call for proposals for standardizing genetic and clinical data and developing new diagnostic methods. Led by Dr. Nunes (U730) (together with the Bellvitge Biomedical Research Institute and the University of Vigo).
- **aHUS/C3g registry:** Registry of patients with atypical uremic hemolytic syndrome and C3 glomerulopathies. Together with the "Iñigo Álvarez de Toledo" Renal Foundation and Dr. Rodríguez de Córdoba's group (U738)-CSIC.
- **Glycogen storage disease type V registry:** Dr. Antoni Andreu (U701) and Dr. Miguel Ángel Martín (U723) have put together a multicentre research team that has prepared a registry with the 239 diagnosed cases in Spain of glycogen storage disease type V, also known as McArdle disease. The phenotype data of this registry, published in the Journal of Neurology, Neurosurgery & Psychiatry, show that symptoms of intolerance to physical exercise increase with age, but are milder in those who have the disease and are physically active.

In summary, updating RD registries is one of the translation activities with the most long-term added value because it allows knowing the epidemiology of these pathologies, This knowledge is biased, however, due to the low prevalence of RD.

Other translational activities: Participation in encounters and meetings with patient associations

A number of CIBERER groups have participated in encounters and meetings with patient associations, such as:

- The association of aid for people with albinism, **ALBA**, organized its **7th Informative Conference** on April 4, 6 and 7 in Huelva. Dr. Lluís Montoliu (U756), member and active collaborator of the association, participated in the encounter. This 7th Informative Conference was dedicated to "Albinism and Sports", and the University of Huelva, the Virgen del Rocío Private Teaching Centre, and many other people and entities who selflessly participated and cooperating in turning the meeting into a

success, all helped. Sports were used at the conference as a meeting point to approach the visual impairment, training, education and health of people with albinism.

- CIBERER (U753) collaborated in the **Scientific Conference on 22q11 for Parents and Professionals**, held at Hospital Universitario La Paz de Madrid on May 11. Specialists from various disciplines will speak about the molecular aspects of this rare disease, psychomotor development and learning, psychiatric problems associated with the syndrome or speech, heart or immune system anomalies. Investigators, healthcare practitioners and family members of patients with the disease attended the conference.
- Sant Pau Hospital de Barcelona hosted a **meeting of spinal muscular atrophy investigators from all over Spain** organized by CIBERER U705 on May 30. Representatives of Units 702, 703, 728 and 755, in addition to 14 other research groups and members of the charitable foundation called FUNDAME, the foundation of families and patients that support research, all attended. In this encounter, a briefing was given about the GENAME project («Defining targets for therapeutic in SMA»), discussing the different publications and doctoral dissertation given, and the perspectives of new collaborations in the diagnosis, translational research and treatment of this disease.
- Dr. Jordi Surrallés, of CIBERER U745-Universidad Autónoma de Barcelona (UAB), and Dr. Juan Bueren, of U710-CIEMAT, organized the **14th meeting of the National Fanconi Anemia Network** at the UAB on June 19. About 60 people attended, including family members of patients, medical specialists and basic investigators. Two parallel meetings were held in the morning: on one hand, family members got together to talk about their respective experiences, and the doctors and basic investigators got together in another different room. During the afternoon session, a joint meeting was held in which family members could ask the specialists the questions they were most interested in.
- **Conference on advancements in the diagnosis, research and therapy of hereditary hypoacusis** organized by Dr. Miguel Ángel Moreno (U728 CIBERER) in collaboration with Isabel Varela-Nieto (U761) and José María Millán (U755), at the University of Alcalá de Henares on September 10. Representatives of the patient associations called FIAPAS and CLAVE also participated in this event. At this conference, patients and professional were informed of the most recent advancements in the genetic diagnosis of this pathology by means of last-generation technologies (massive sequencing and microarrays) and the study of the mechanisms of pathogenesis involved as a basis for developing therapies.
- **Informative meeting about the pathologies associated with Fragile X Syndrome premutation**, held on September 29 in Madrid. It was organized by Dr. Montserrat Milà and Dr. Laia Rodríguez-Revenga, from CIBERER U726. Different diagnostic and treatment aspects and recent research were discussed in this encounter with patients and family members. This meeting is comprised within an intramural programme of the CIBERER.
- **1st National Encounter of Families with Children with Mitochondrial Disease**, held in the CREER of Burgos November 13-17, with the participation of Dr. Julio Montoya (U727), Dr. Miguel Ángel Martín (U723), Dr. José Antonio Sánchez (U729) and Dr. Cecilia Jiménez-Mallebrera (U703). Lectures about mitochondrial diseases and the research being conducted on them were given in this encounter. Several lectures also related to rehabilitation, orthopedics, music therapy and therapy with dogs.

• The **3rd National Encounter of acromegaly patients** brought together over 80 patients, investigators and healthcare practitioners, and was held on December 14 and 15 in Seville. Practical topics of interest for patients, such as neurocognitive aspects and prevention of the more prevalent cancers in acromegaly patients, familial acromegaly, when the genetic study or research and innovation in relation to new treatments is necessary, were discussed at this event, with the participation of Dr. Eugenia Resmini (U747 CIBERER).

Dissemination of CIBERER translational activity

Given that the Spanish Government declared 2013 to be the **"Spanish Year for Rare Diseases"**, all the events in which the CIBERER participated were comprised in that same year so they included the logotype created for that purpose.

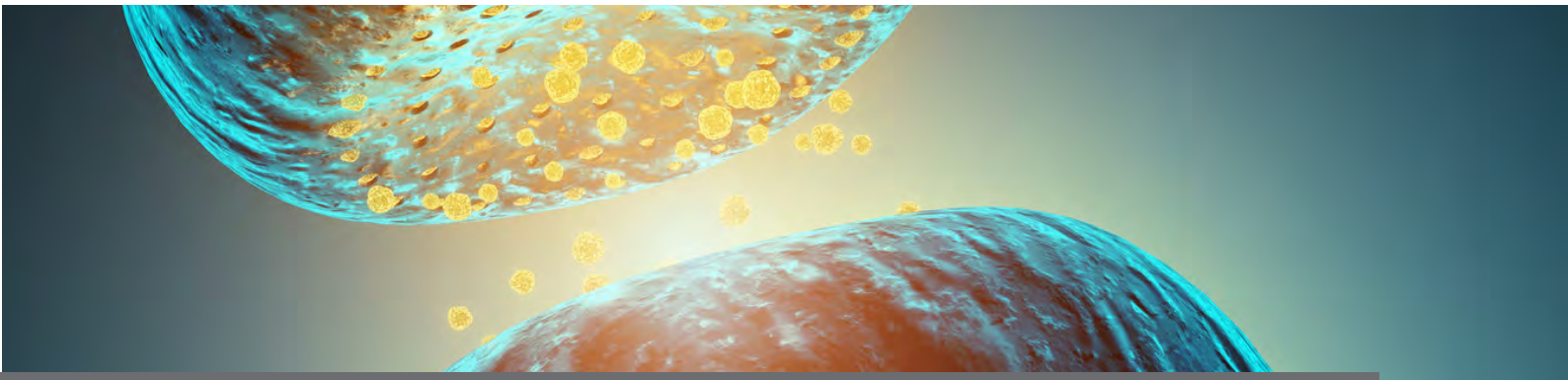
The quintessential act for the dissemination of the CIBERER translational activity is the **Conference entitled "Investigar es Avanzar" (To conduct research is to move forward)** held within the framework of the events for the World Rare Disease Day. CIBERER organized the fifth **Conference "Investigar es Avanzar"** on February 27 in Madrid. Investigators and patients discussed their lines of collaboration in neuromuscular pathologies and Lowe syndrome. Furthermore, CIBERER investigators discussed the usefulness of genetic counseling for patients suffering rare diseases and the results of 36 years of the first Spanish registry of a large group of rare diseases: congenital anomalies. This event has also provided the opportunity for CIBERER investigators and the corresponding FEDER counterparts to talk about their collaboration in research.

The **8th Translational Research and Personalized Medicine Meeting** was also held on February 7, 2013 at the Fundación Jiménez Díaz de Madrid. The conference was organized by U704, led by Dr. Ayuso, with the collaboration of the Roche Institute.

The fourth installment of the **"CIBERER DNA Day"**, held at La Paz University Hospital on April 29, focused on the use of NGS in healthcare. This conference was led by Dr. Pablo Lapunzina and Dr. Julián Nevado, from CIBERER U753.

The Ministry of Health, Social Services and Equality organized a scientific conference on translational research, research challenges and actions of the Carlos III Health Institute (ISCIII) in RD on October 24 entitled **«Conocer la rareza, mejorar nuestras vidas»** (Know the anomaly, improve our lives) with the collaboration of ISCIII, Dr. Pablo Lapunzina (U753), Dr. Francesc Palau (U732), Dr. Francesc Cardellach (U722), Dr. Eduardo Tizzano (U705), Dr. Roberto Zarrabeitia (U707), Dr. Carmen Ayuso (U704), Dr. Belén Pérez (U746) and Dr. Manuel Posada (U758), all from CIBERER, participated in this encounter as moderators and speakers.

Finally, CIBERER together with the other 8 Networking Biomedical Research Centres (NBRCs) disclosed eight practical cases of scientific advancements achieved with the networking research of excellence at a round table held in Barcelona in the framework of Science Week. Dr. Elisenda Eixarch, coordinator of line of research of the Fetal Medicine Research Center and assigned to CIBERER U719, led by Dr. Eduard Gratacós, presented her translational research in fetal medicine at a round table organized by the NBRC at the CEK in Barcelona on November 18. At this event, each of the NBRCs disclosed a specific case of translational research serving patients.



Transfer Programme

Description

In recent years, CIBERER has established strategic alliances with particularly important agents in approaching the productive sector relating to RD, such as ASEBIO (Spanish Association of Biocompanies), and biotechnological companies or pharmaceutical companies.

Boosting the RD knowledge transfer to the productive sector is a fundamental objective identified by CIBERER. Advancement in the scientific activity of the research groups must continue, and the economic investments made in research must be returned to society.

Objectives

CIBERER is a national and international leader in research on and knowledge about RD, and works to directly and effectively strengthen relationships with the productive sector keeping 2 clear objectives in mind:

Consolidation of tools for suitable knowledge transfer processes.

Promoting RD knowledge transfer activities and innovation.

Resources used

Staff resources: Transfer Manager with the support of the team of Scientific Activity Managers.

Support from the company Clarke, Modet & Co.

Services: Management Office.

Results

Patents

One of the primary objectives of CIBERER is to promote transferring complementary knowledge to the already existing programmes in the Consortium Institutions. This drive to transfer knowledge is fundamental because of the advantages it involves for both research groups and for society as a whole.

We would first like to highlight the following patents application filed in 2013 in collaboration with some of the institutions forming the consortium:

Group	Application No.	Title
National		
U757	P201331573	GSE24.2 peptide derivatives to treat diseases caused by oxidative stress and damage to DNA
U757	P201330131	Biodegradable bionanoparticles for the release of the GSE24-2 peptide, method for obtaining same and use thereof
International		
U756	PCT/ES2013/070592	New animal achromatopsia model
U757	PCT/ES2013/070581	Release of substances into senescent cells

The primary activities for promoting the Transfer performed by CIBERER are the following:

Development of tools for transfer processes

First, CIBERER continues providing advisory services relating to intellectual property and other aspects relating to the transfer. This task was coordinated by Scientific Management with the support of the company Clarke, Modet & Co. Investigators channeled all their queries relating to the protection of R&D&I activities generated while carrying out their projects, and received guidance and support about applying good practices in management the measures for protecting project results. The following situations in which Clarke, Modet & Co. offered support to CIBERER groups in 2013 stand out: evaluation of the patentability of certain diagnostic methods, different queries about creating a spin-off in the biomedical field and aspects relating to marketing research results, queries about an orphan drug or drafting a CIBERER patent. They have also provided advisory services to the department of managers by evaluating the portfolio patents in which CIBERER participates to offer an estimate/forecast of expenses resulting from said patents.

We have also worked to identify and assess goods and services of the different CIBERER groups with transfer potential.

CIBERER is a full member of ASEBIO (Spanish Association of Biocompanies). In 2013, CIBERER continued its activity within the Innovate Drug group, the specific Rare Diseases and Advanced Therapies subgroups, as well as in the Molecular Diagnosis Work Group, actively participating in the different meetings. Since 2011, CIBERER has also been an associate member of BIOVAL (Bioregion of the Community of Valencia). AND since the year 2013 is partner collaborator of the Technologies Medical and Health Innovation (ITEMAS) Platform. The ITEMAS Platform seeks to encourage innovation in health technology as a fundamental tool to make the National Health System more sustainable, supporting the development of the innovative culture necessary to facilitate integrating the science-industry system in the field of medical technology.

Participation in forums and events enabling collaboration with the private sector

Finally, in 2013 the Management Office staff and the CIBERER Management attended and participated in other forums and events of particular interest enabling some type of collaboration with the private sector, such as:

- **TRANSFIERE** which took place on February 13-14, 2013 in Malaga. CIBERER was represented by Dr. Juan Luque, CIBERER Scientific Manager.
- **6th International Conference on Orphan Drugs**, which took place on February 14-16, 2013 in Seville. Dr. Merche Serrano as well as managers Mónica Bescos and Juan Luque, were invited to attend said event to explain the activity that CIBERER is performing.
- **"Symposium biobanks and biomedical collections an ethical framework for future research"**, which took place on June 19-20, 2012 in Strasbourg, France. Dr. Palau, CIBERER Scientific Director, attended this event organized by the European Council on behalf of CIBERER.
- **Annual Meeting of the European Society of Human Genetics** (ESHg), which took place on June 23-26, 2012 in Nuremberg, Germany. A number of CIBERER investigators participated in the meeting, included Dr. Palau.
- **V Spanish Drug Discovery Network Meeting**, which took place in the Science Park of the Universidad de Valencia, October 24-25, 2013. Dr. Juan Luque, CIBERER Scientific Manager, was present at this event.

Furthermore, CIBERER has co-organized and participated in several conference and workshops in collaboration with companies to deal with different aspects relating to the etiology, causes, clinical symptoms and treatment of RD:

- **Día Mundial de las Enfermedades Raras "Investigar es avanzar"** in the CECA, Madrid. Several companies and institutions representing the private sector attended.
- **8th International Meeting on Translational Research and Personalized Medicine: Genomic Medicine in hospitals in the 21st Century**, Fundación Jiménez Díaz de Madrid with the collaboration of Roche Institute.
- **DNA-Day CIBERER Workshop** at Hospital Universitario La Paz de Madrid with the collaboration of Roche, Genicell Biotech, Sistemas Genómicos, Agilent Technologies, Abyntek, Progenika and Perkin Elmer.
- **27th National Conference of the Spanish Association of Human Genetics**. A number of research groups from CIBERER and from the field of rare diseases were represented at this event.
- **3rd Conference of the Group for Rare Diseases in Adults**. This conference was held at Hospital Clínic de Barcelona and Genzyme and Actelion collaborated in it.
- **12th International Congress of Inborn Errors of Metabolism (ICIEM 2013)**. CIBERER collaborated in this international event in which 20 companies from the pharmaceutical and biotech sectors participated.
- **Conference on pharmacological chaperones in lysosomal diseases and other applications**. Held at the Biomedical Research Centre of Aragon (CIBA) C Zaragoza with the participation of Alexion.

Other RD Knowledge and Innovation transfer activities

As part of the continuous activity of 2013, public-private collaboration was encouraged through work meetings with private companies or entities to present specific opportunities to collaborate with CIBERER. A number of meetings were held to explore the collaboration pathways in future projects. The contracted companies include: Amadix, Biorray, Cabana genetics, CRB Inverbio, Valentia Biopharma, Janus Developments and Merck Serono.

One-time agreements were also maintained with different companies for R&D collaboration.

- Collaboration agreement with Sistemas Genómicos, S.L to manage samples obtained by Sistemas Genómicos, S.L. and the assignment thereof to CIBERER-BIOBANK.
- Agreement with EVERIS to participate in the collaborative AMER project in the CDTI Innterconecta call for proposals.

4

Transversal Platforms

to support Research and Common Infrastructures

Orphanet

CIBERER been Orphanet's Spanish partner since April 2010. Orphanet is the information portal of reference in relation to rare diseases and orphan drugs and is present in about 40 countries, most of which are in Europe.

The Orphanet portal today as a database of reference in Europe for RD and orphan drugs, pools together information on 9,264 diseases, 6,545 queries specializing in pathologies with a low prevalence, 2,557 patient associations, 19,544 health professionals, and 1,668 laboratories from 37 countries (December 20, 2013). It has an average of 30,000 visitors a day.

In 2013, the Spanish team has a project manager, Dr. Corrochano, and two scientific documentalists, Martín Arlés and Mª Elena Mateo. The Orphanet-Spain Scientific Committee, which is responsible for validating most of the information generated in Spain, currently has 59 experts integrated in 30 different medical areas. The complete list of members of the Spanish Scientific Committee can be consulted at the following link:

http://www.orphanet-espana.es/national/data/ES-ES/www/uploads/ComiteCientifico.pdf

The Orphanet Platform carried out the following activities in 2013:

Data Collection and Update

The team is responsible for continuously collecting and updating the directory listing the services offered in Spain. The following document includes the inclusion criteria and the sources of information used for each type of activity that is recorded:

http://www.orphanet-espana.es/national/data/ES-ES/www/uploads/criterios-ES.pdf

After the process of collecting and updating data throughout 2013, the Spanish activities included in the Orphanet database are the following:

Total of Spanish Activities in 2013	
Specialized clinical queries	423
Patient associations	666
Diagnostic tests	6743
Clinical trials	666
Research projects	423
Registries/Biobanks	66

Translations

A total of 286 disease summaries and 1,177 names of new RD have been translated to Spanish and incorporated in the web page.

To contribute to the translation of the Orphanet Patient Encyclopedia, a series of texts containing abundant information about a number of RD written so that the general public can understand it, CIBERER has allocated of part of the budget for this platform to translating and validating 12 of these articles, all of which are pending publication.

Promoting active participation of the Scientific Committee (SC)

Scientific Committee (SC) members were involved in different tasks in 2013, such as reviewing disease summaries, clinical guidelines belonging to Orphanet and external guidelines and the directories of expert centres. They were also involved in answering patient queries.

Promoting the communication and dissemination plan

Greater dissemination of the Orphanet project is essential for giving the portal greater exposure and therefore maximizing its usefulness. The following actions, among others, have been boosted for that purpose:

- Participation as teachers in the following courses:

  - Official Master's in "Current Knowledge on Rare Diseases", Universidad Internacional de Sevilla, Seville, March 20.

  - Course entitled "Rare Diseases: Research, clinical care and social awareness", Escuela de Estudios de Salud de Valencia, Valencia, September 9.

- Orphanet- Spain staff together with CIBERER managers handle queries submitted by people with RD, and forward them to different experts on the Orphanet Scientific Committee depending on the pathology in question. The graph shows that more than a third of the queries made by people with rare diseases reach CIBERER through the Orphanet web.
- Contributions to the Orphanews Europe newsletter.
- Maintenance of the Orphanet Spain web:

  The Orphanet-Spain web page, which is developed by the Spanish team of documentalists and transmits current situation, events and documentation of Orphanet, which are all relevant on a national level, published about 120 articles throughout 2013. In collaboration with patient associations, it advertised events relating to RD in Spain, particularly those relating to Rare Disease Day. It also provided access to documents in Spanish on these diseases, such as the various guidelines contained in the "Enciclopedia de Orphanet-España" (Orphanet-Spain Encyclopedia), or specific documental resources to offer social, educational and health support for people suffering from rare diseases in Spain, compiled in the "Other resources" section.

Promoting resources shared by CIBERER and Orphanet, working so that the relationship between the Institutions is an added value for their respective projects

In 2013:

- The list of rare diseases that CIBERER works with was reviewed and updated.
- Collaboration was offered to the Patient Care Service in managing of queries and information requests by patients.
- All the CIBERER Research Programmes (RPs) have collaborated with Orphanet by updating the activities they carry out in the CIBERER database, which in turn serves to update the Orphanet platform.
- Additionally, CIBERER investigators belonging to different units (U703, U704, U712, U735, U752, U753 and U755) have collaborated with Orphanet in a number of ways, such as by reviewing/writing summaries and clinical guidelines.

CIBERER Biobank

The activities carried out by CIBERER Biobank are consistent with the strategic objectives included in the 2013 Action Plan and they aim to promote proper platform operation. Overall, the following points stand out:

- In 2013 the process of implementing a Quality Management System (QMS) of the Biobank according to the ISO 9001:2008 standard, obtaining AENOR certification in November.
- A new sample processing technique has been implemented, and external services have been fine-tuned.
- The Biobank's work has been disseminated in various national and international forums.
- In 2013, the Biobank's participation in several national and international projects was encouraged.

As regards the Biobank's objectives defined in the 2013 Action Plan, the following stands out:

Objective 1: To provide biological samples to the Biobank

• Campaign from prospective quality samples for use in research

The Biobank received samples from different hospital services from centres such as Hospital Universitario La Fe de Valencia, La Paz Hospital de Madrid, Hospital Clínic de Barcelona or the Jiménez-Díaz Foundation.

A campaign was started up this year to obtain samples of RD aimed at CIBERER investigators. As a result, 3 expressions of interest by CIBERER groups were received and the sample collection process started after evaluating the suitability of said samples.

Besides the samples collected through the campaign, different CIBERER groups expressed their interest in collaborating with the Biobank in the Action Plans pertaining to the medical subject matters to which they belong. That interest is manifested in sending samples and requesting services.

A total of 105 samples from 22 different pathologies were collected in 2013. The biological material catalog can be consulted at Biobank's web page: http://www.CIBERER-biobank.es

Objective 2: To promote a Strategic Alliance and Dissemination Plan

• Affiliation and collaboration with national and international biobank networks

CIBERER Biobank:

- continued collaborating with the Biobank Network of Valencia in which it is integrated;
- signed a Specific Collaboration Agreement with the Public Health Research Centre for locating the Biobank in said centre's facilities;
- signed an Agreement (July 2012) with Sistemas Genómicos that is still in force to send samples of RD to the CIBERER Biobank from clinics of Sistemas Genómicos;
- participated in the Work Group of Blood Derivatives of the National Biobank Network;
- participated as an 'Associated Partner' in a 7PM project (HEALTH.2012.2.1.11-C: databases, biobanks and clinical bio-informatics hub for rare diseases) coordinated byH. Lochmüller, of Newcastle University;

• Disseminating information about Biobank activity

The biobank participated in six conference/meetings in 2013, dissemination information about its activities (RD-Connect kick off meeting; 6th Annual CIBERER Meeting; 2nd TREAT-CMT Scientific Meeting; presentation of the Biobank in the International Conference on Glycogen Storage Disease in Barcelona; BBMRI Conference; Annual Meeting of the National Biobank Network).

Objective 3: To generate added value for CIBERER groups

CIBERER groups value the importance of having the Biobank platform within the network. In 2013 several expressions of interest in collaborating with the Biobank were submitted by CIBERER groups, including:

- **Group: U704. Dra. Ayuso / Dra. Marta Cortón**.- Collaboration in immortalizing cell lines.
- **Group: U730. Dr. Nunes/Dr. Miguel López de Heredia**.- In the framework of an international project (European and North American groups) to study Wolfram syndrome, samples of DNA, RNA and immortalized cell lines will be collected (from about 30 patients). CIBERER Biobank will handle processing, storing and safeguarding these samples.
- **Group: U733. Dr. Pallardó/Dr. José Luis García**.- The Biobank collects and manages samples for two projects led by these investigators.
- **Group: U745. Dr. J. Surrallés/Dr. María José Ramírez**.- Collaboration in immortalizing cell lines of patients with Fanconi anemia.
- **Group: U753. Dr. Pablo Lapunzina**.- Collaboration in immortalizing cell lines of patients with different pathologies.
- **Group: U760 Dr. Víctor L. Ruiz.**- Collaboration in immortalizing cell lines of patients with different pathologies.

• Services Provided

The Biobank has fine-tuned a lymphocyte immortalization service that all CIBERER investigators can benefit from and is fine tuning other techniques that can also be offered as a service (myoblast culture, iPS cell generation,..).

Thirteen requests were received from CIBERER groups in 2013.

Objective 4: To promote and support new lines of action in rare diseases

Participation in projects:

- In 2013, the Biobank continued collaborating in projects which began in previous years and started working in other new projects:
- Open phase II study of ketoconazole as an inhibitor of the enzyme CYP17 in locally advanced or disseminated granulosa cell tumors of the ovary. GreKo Study. Applicant: Fundación Hospital Universitario de Alcorcón. Principal investigator: Jesús García-Donas Jiménez. Project funded by the General Directorate of Pharmaceuticals and Medical Devices, Ministry of Health and Social Policy.
- FP7 HEALTH 2012-INNOVATION: RD-Connect: An integrated platform connecting registries, biobanks and clinical bioinformatics for RD. The biobank participates as an Associated Partner.
- Translational Research, Experimental Medicine and Therapeutics on Charcot-Marie-Tooth, TREAT-CMT. International Rare Diseases Research Consortium (IRDIRC).
- Participation, together with the CIBERER U730 (Dr. Nunes), in an international project (European and North American groups) to study the Wolfram syndrome. In the framework of this study, samples of DNA, RNA and immortalized cell lines will be collected (from about 30 patients. CIBERER Biobank will handle processing, storing and safeguarding these samples.
- Effect of epigenetic factors on the development of the juvenile idiopathic scoliosis. José Luis García Giménez (U733). Grant Call 2012 of Mapfre Foundation.

Networking Laboratory Animal Phenotyping Service (SEFALer)

The Networking Laboratory Animal Phenotyping Service (SEFALer) is coordinated by CIBERER through several of its research groups specialized in phenotyping animal models with a specific application for rare diseases.

SEFALer's main objective is to characterize the phenotype of animal models of rare diseases as a fundamental tool to studying the physiopathology, to understanding the underlying molecular mechanisms, to identify diagnostic criteria and to evaluate and refine new therapies. SEFALer provides significant support to the research activity of CIBERER units.

The activities carried out in 2013 based on the objectives proposed for the year in each are described below:

Objective 1: To increase the phenotyping offer and SEFALer's activity

In 2012 data from a survey conducted on all the CIBERER units was analyzed to compile information about the demand for phenotyping tests.

Certain specific measures were taken based on the results:

- To increase SEFALer's offer, meeting the demand of CIBERER investigators to the greatest extent possible.
- To periodically repeat surveys.
- To make it easier for interested units to join SEFALer.

Two new units become full members of SEFALer in 2013:

- **SEFALer Unit F5**

  Neurometabolic Disease Laboratory of the Bellvitge Biomedical Research Institute (IDIBELL). CIBERER Unit 759, led by Dr. Aurora Pujol.

- **Unidad SEFALer F6**

  Animal models by genetic manipulation of the National Biotechnology Centre (CNB). CIBERER unit 756, led by Dr. Lluís Montoliu.

  At the same time, we continued to search for information about other phenotyping groups or services outside CIBERER and this information has been progressively included on the SEFALer portal:

  http://www.ciberer.es/index.php?option=com_content&task=view&id=308&Itemid=204

Objective 2: To improve communication and coordination between SEFALer units.

SEFALer units maintain communication through the service's web page and email, sefaler@CIBERER.es, which includes information about its activity, acting like a networking service. They also hold group meetings, taking advantage of the annual CIBERER meetings and SEFALer training courses.

SEFALer units can act in a coordinated manner to share animals and perform complete phenotyping on the animal model.

Objective 3: To improve relations with other NCRC or RETICS groups.

In 2013 relations were maintained with research support groups and services that are outside CIBERER, belong to other NBRCs or RETICS and perform phenotyping activities on animal models for the mid-term establishment of a national animal model phenotyping network, particularly for rare diseases. The biggest upcoming challenge will be to integrate new nodes in the new NBRC structure that this service will be a part of.

Objective 4: To improve exposure of SEFALer activity.

The SEFALer web page was kept updated in 2013 with monthly notifications and information useful for CIBERER investigators. Relevant service activity has also been included in the "highlighted information" section on the CIBERER portal (publications, organization of training courses, participation in events, etc.). It can be asserted that the knowledge possessed by CIBERER units about the SEFALer activity and offer has considerably increased this year. Proof of this is the increase in applications for trials by CIBERER investigators.

In addition, continuous presence in different scientific forums and associations relating to animal experiments, animal models, biomedical research, research in rare diseases, etc., was maintained. Specifically, exposure has been given to SEFALer in other NBRCs (CIBERObn, CIBERDEM, CIBERSM and CIBERNed), in scientific associations (SEEBM, SENC, SEBC, SECAL, IBRO, ARO, etc.) and in national research centres (CSIC, CRG, CNIO, universities, etc.) and international research centres such as the Mouse Clinic (ICS) or the UCL Ear Institute. Fluid contact has also been maintained with some of the large-scale phenotyping centres of the network (Wellcome Cambridge, ICS Strasbourg, GMC Helmholtz, etc.).

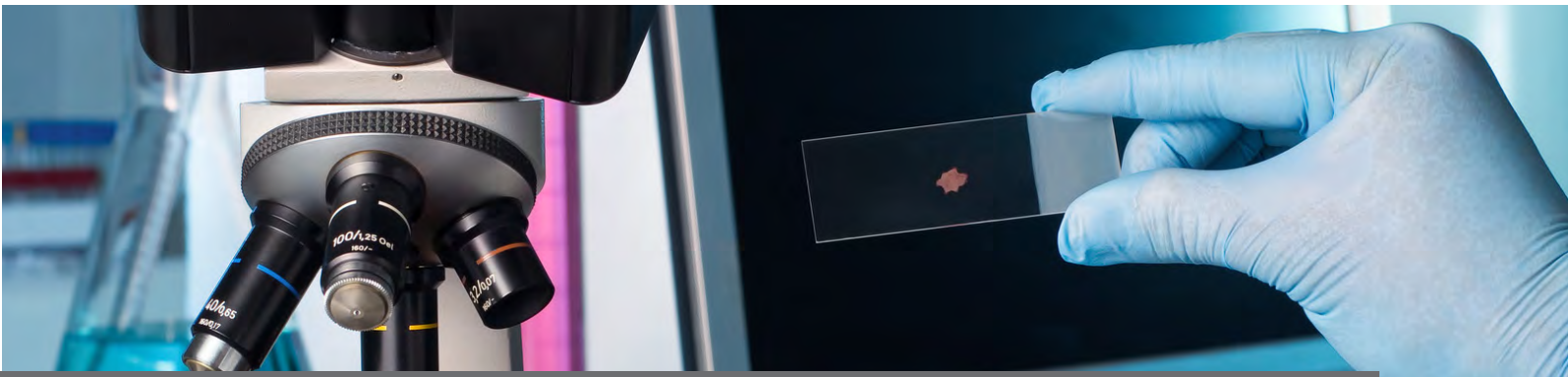
Objective 5: To maintain and enhance the advisory and informatory activities.

The SEFALer portal is a fundamental tool for the network. In 2013, the "News" and "Courses, Conferences and Workshops" section has been maintained and periodically updated with information of interest about phenotyping with the collaboration of CIBERER managers. Presentations of training courses organized by SEFALer have also been added to the web page.

Queries made by CIBERER investigators and by investigators outside CIBERER relating to animal model phenotyping, primarily by direct telephone contact and by e-mail at sefaler@CIBERER.es have also been attended to.

Objective 6: To maintain and improve the Training Plan

SEFALer continues giving at least one annual course on animal model phenotyping. The third installment of the "ANIMAL MODEL PHENOTYPING" course was successfully held on December 9-13, 2013 in the School of Veterinary Medicine of the Universidad Complutense de Madrid, in which several SEFALer units participated.



Bioinformatics Platform for Rare Diseases (BIER)

The Bioinformatics Platform for Rare Diseases (BIER) is a transverse Work Group whose primary mission is to collaborate with the experimental groups working with genomic data, offering them both IT and scientific support for the analysis and interpretation of said data.

The basis for this platform is the technical knowledge and strong lines of research of the CIBERER bioinformatics groups: functional genomics and genomic, transcriptomic and massive sequencing data analysis conducted by U715, led by Dr. Joaquín Dopazo, and the experience in proteomics and systems biology conducted by U741, led by Dr. Francisca Sánchez.

BIER began operating in 2012 and has become a binding and synergistic element within CIBERER. This involves promoting the formation of small temporary groups to work on common collaborative projects and incorporate groups with bioinformatic-related interests into the collaboration structure of the BIER.

Massive sequencing has led to a new generation of data in many CIBERER group laboratories that is hard to handle, hard to interpret, and requires bioinformatics. This trend is also a clearly growing trend. In 2011 CIBERER started up a Programme on "Genes in Undiagnosed Rare Diseases" that has led to a series of projects to reinforce the lines of work of the research groups in this regard to respond to a cases of samples from patients that still had no identified genetic diagnosis.

Finally, the peculiarity of RD is that the availability of few samples in a genomic scenario requires developing methodologies of analysis and specific bioinformatic tools that are not available in conventional bioinformatics.

In this regard, the actions performed by the platform in 2013 include:

Objective 1: To give exposure to BIER, both within CIBERER and outside it

- Maintain the specific informative web page with available analysis tools.
- Create a beta version of an online tool for filtering genomic variants, public launch being slated for 2014.
- The system facilitating and enabling support for groups was maintained, primarily based on a collaborative plan, within the possibilities of the BIER.

Objective 2: To support CIBERER's work in top-level competitive strategic fields:

- Support was offered to analyze ultrasequencing data of the CNAG (National Genomic Analysis Centre) and MGP (Medical Genome Product) from the familial genomic analysis project initiative promoted by CIBERER.
- More specific support was offered in the required cases: support at different levels, starting with primary data processing up until applying more sophisticated techniques with predictive target function and locating potential, such as applying different functional prediction methods and other methods based on interaction network mining, for example.
- Large-scale genotyping, transcriptomics with microarrays or RNA-seq, proteome analysis and their projection on interactomes, etc., were performed for some projects.

Objective 3: To generate added value by encouraging collaborations between CIBERER groups.

This objective contemplates collaboration with CIBERER research groups for the joint development of intramural research projects and other types of research projects.

Several levels of aid offered throughout 2013 stand out among the collaborations with CIBERER groups:

- Advisory projects: BIER offered advisory services about analysis tools to be used to groups of expertise.
- Support projects: BIER has provided support and been involved in analyzing genomic data of one or several groups.
- Development projects: CIBERER groups suggested a development that BIER carried out.

The BIER platform aspires to have a high degree of interaction with Orphanet because a great deal of the information contained in this international database can be used for completing information about RD and their possible etiologies, genetic origin, symptomatology interrelation, etc., enabling an integrative study of diseases. In addition, many of the analysis tools could in turn be implemented in Orphanet. For now, this interrelation is still incipient.

Finally, the BIER platform sought to train CIBERER investigators in bioinformatic applications relating to the analysis of genomic data. In this regard in 2013:

Objective 4: Training through courses or internships.

- The PhenUMA course "Introduction to the analysis of phenotypic and functional networks in rare diseases" coordinated by U741 investigators was organized at the University of Malaga.
- Through the CIBERER mobility programme, BIER received 12 CIBERER investigators in its work centre, 8 of them group leaders and four others who benefited from CIBERER training aids for intramural mobility. With these short internships

and visits, real case studies could be analyzed and the data from these studies could be analyzed with bioinformatic tools by means of the complementary knowledge of both parties.

Publications directly resulting from BIER activity besides those led by groups supported by the data filtering and interpretation done by BIER:

- García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, Bodoy S, Merinero B, López-Sala A, Dopazo J, Nunes V, Ugarte M, Artuch R, Palacín M, Rodríguez-Pombo P. Two Novel Mutations in the BCKDK Gene (Branched-Chain Keto-Acid Dehydrogenase Kinase) are Responsible of a Neurobehavioral Deficit in two Pediatric Unrelated Patients. Hum. Mutat. 2014.
- de Castro-Miró M, Pomares E, Lorés-Motta L, Tonda R, Dopazo J, Marfany G, Gonzàlez-Duarte R. Combined genetic and high-throughput strategies for molecular diagnosis of inherited retinal dystrophies. PLoS ONE. 2014; 9(2):e88410.
- Tort F, García-Silva MT, Ferrer-Cortès X, Navarro-Sastre A, García-Villoria J, Coll MJ, Vidal E, Jiménez-Almazán J, Dopazo J, Briones P, Elpeleg O, Ribes A. Exome sequencing identifies a new mutation in SERAC1 in a patient with 3-methylglutaconic aciduria. Mol. Genet. Metab. 2013; 110: 73–77.
- González-del Pozo M, Méndez-Vidal C, Santoyo-López J, Vela-Boza A, Bravo-Gil N, Rueda A, García-Alonso L, Vázquez-Marouschek C, Dopazo J, Borrego S, Antiñolo G. Whole-exome sequencing identifies novel compound heterozygous mutations in USH2A in Spanish patients with autosomal recessive retinitis pigmentosa. Mol. Vis. 2013;19:2187-95.
- Medina I, Salavert F, Sanchez R, De Maria A, Alonso R, Escobar P, Bleda M, Dopazo J. Genome Maps, a new generation genome browser." Nucleic Acids Res. 2013; 41:W41-W46.

PROTEOmAb

PROTEOmAb
FENOTIPADO DEL METABOLISMO ENERGÉTICO MEDIANTE TECNOLOGÍA DE ARRAY DE PROTEÍNAS

PROTEOmAb is an energy metabolism phenotyping platform using protein array technology. It is located in CIBERER unit U713 UAM Severo Ochoa Molecular Biology Centre led by Dr. José María Cuezva. The group has ample experience in this methodology that it has been offering as a service to the scientific community since 2012. It offers a service comprising the quantitative analysis of energy metabolism proteins in biological samples in a simple and reproducible manner using high-affinity and high-specificity monoclonal antibodies (mAbs).

Methodology: The analysis can be done on collections of up to 1,000 different biopsies, which allows establishing correlations with clinical parameters and parameters of response to certain treatments. A reverse-phase protein microarray platform is used, which allows quantifying the expression of energy metabolism proteins in biopsies of normal and pathological tissues.

PROTEOmAb services

- Identification and validation of molecular markers of the disease and of the response to therapy.
- Identification of new diagnostic markers.
- Establishing correlations between biomarkers and disease progression.
- Establishing correlations between biomarkers and response to a treatment specific.

PROTEOmAb collaborations/services developed

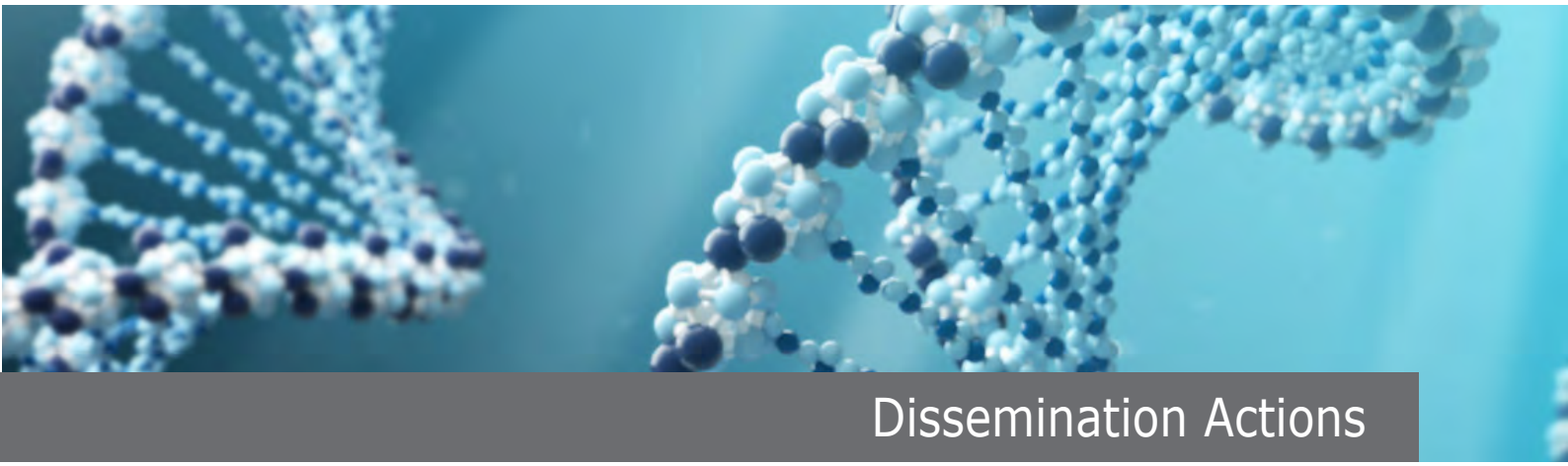
Collaborations have been established with various NBRC groups and with other institutions:

- Dr. Lourdes Ruiz Desviat, Universidad Autónoma de Madrid, CIBERER U746 and Dr. Barry Michel, Mayo Clinic, Rochester, USA. Pathology studied: Propionic acidemia.
- Dr. Francesc Cardellach López, Hospital Clínic de Barcelona, CIBERER U722. Pathology studied: All myositis variants: dermatomyositis, polymyositis and myositis with inclusion bodies.
- Dr. Miguel A. Martín Casanueva, 12 de Octubre Hospital Research Institute (i+12), Madrid, CIBERER U723. Pathology studied: Mitochondriopathies due to Complex I deficiency.

5 Scientific Activity

Specific of CIBERER (Result as a consortium)

Information about mobility and training actions can be consulted in the specific "Training Programme" section.



Dissemination Actions

With its Communication plan, CIBERER continuously informed the society about the work of the research groups, their projects, the diseases they are researching and the new knowledge generated. Patients and support associations are the main targets of these communication actions.

For the dissemination activities, the CIBERER Communication Department maintained continuous contact with the press, has prepared a scientific newsletter and a social newsletter, has managed a Twitter account and kept the CIBERER web updated.

CIBERER has also directly approached patients and their families with the periodic organization of conferences or with their presence in scientific, institutional and social forums relating to RD.

The CIBERER Communication Plan is split into two large lines of action, the Internal Communication Service and the External Communication Service.

Internal Communication Service

With this service and through the investigators and professionals associated with the institution, CIBERER consolidated its activity and corporate image and brought together its networking structure.

CIBERER worked hard to turn its web page (www.ciberer.es) into an effective instrument. All the calls for proposals (use, training, aid programmes, etc.) that may be of interest for the groups, all the events organized by CIBERER or relating to RD, updated news relating to the Institution and press clips available on the Intranet have been included. This web page was updated every day.

The CIBERER Electronic Newsletter must also be highlighted. It is a very effective publication, on one hand, for disseminating the research in RD conducted by CIBERER and on the other, for providing all the information of interest about RD to investigators that are both hired by and affiliated with our Institution.

Therefore, in 2013 work was done to improve knowledge among the different CIBERER research groups and to maintain their scientific collaboration links.

Most noteworthy activities performed in 2013:

- The Intranet, which is constantly updated with scientific and institutional information of interest for the CIBERER investigators, has become a tool at the service of its activity. It received 13,205 visits in 2013.

- The Electronic Newsletter used to periodically report CIBERER activity to associated investigators and also to external directors interested in RD. 7 electronic newsletters were sent out.
- Services over the web and Intranet for communicating funding opportunities and events for research on RD. The Management Office is responsible for updating all the news and events of interest for the research groups every day, promoting the use of the web and the Intranet as a fundamental tool in CIBERER.

External Communication Service

The Communication Service has offered support to investigators so that their activity can be better understood both by people suffering from RD and by society as a whole. With its External Communication Service, CIBERER has transmitted the scientific activity of its research groups, social and institutional activity of the Institution and the events it organized, in order to bring it closer to the reality of patients and family members.

CIBERER has used various means for that purpose. The Communication Department has acted as a press office, carrying out dissemination campaigns intended for the press and dealing with information professionals. CIBERER has also organized dissemination events and updated its web page every day to turn it into an effective communication platform on both an external and internal level. It has also periodically sent out the Social Newsletter, an electronic publication for providing all the information about CIBERER and its research in RD to patients, associations that represent them and to anyone else interested in this field. Since October 2011, CIBERER has also had an active Twitter account which it uses to interact with investigators, patients and the remaining groups of interest in RD.

Most noteworthy activities performed in 2013:

- Daily CIBERER web update, turning it into a dynamic communication tool that includes ongoing research, events calendar, funding opportunities and other information of interest about RD. In 2013, the web was visited by 69,556 users (measured by Google Analytics).
- In 2013, CIBERER had 1,002 hits in the press. This indicator clearly shows that it has become an unquestionable social reference in the field of research in Rare Diseases. In 2013, CIBERER had 28% more hits than in 2012.
- Organization of the fifth conference entitled "Investigar es Avanzar" for the dissemination of CIBERER research activity in the framework of the RD Day. The act was organized in February in Madrid, and it was also given significant coverage in the press.
- Social Newsletter, used to provide information about RD of interest to patient associations and other groups associated with these pathologies and/or with research into them in a simple and comprehensible manner. In 2013, 6 social newsletters were sent out.
- Dissemination of the centre's events, research and activities to the outside world by carrying out press campaigns and continuing handling the press as a communication office. Eleven press campaigns were carried out in 2013.
- Representation of the CIBERER at the patient association conference.
- CIBERER Twitter account, with 1,943 followers.

Appearances in the press

Some of the 1,002 appearances in 2013 are highlighted below in chronological order:

- Feature in Diario Médico about the future of the NBRC. January 21, 2013.
- Feature about Wolfram syndrome including an interview with Virginia Nunes in EFE Salud. January 28, 2013.
- Article in El Mundo about the clinical trial with gene therapy for Fanconi anemia. January 29, 2013.
- Feature in El País about crowdfunding explaining how funding is raised for the Mercedes Serrano group for the I Lowe You project. February 24, 2013.
- Interview on TVE Canarias with Eduardo Salido. February 28, 2013.
- Feature in Diario Médico about rare diseases including interviews with María Luisa Martínez-Frías and Jordi Cruz in the Conference "Investigar es Avanzar" of CIBERER. March 1, 2013.
- Antena 3 news about the discovery of DNA including interview with Francesc Palau. April 8, 2013.
- News in La Vanguardia about research conducted by Jordi Surrallés which identifies the gene regulating three diseases. April 25, 2013.
- News in El Periódico de Catalunya about research conducted by Eugenia Resmini which approaches the relationship between the stress hormone and cured Cushing's syndrome.
- Interview in the programme "Para Todos La 2" aired by TVE with Mercedes Serrano and Manuel Armayones. May 24, 2013.
- News in Las Provincias about a $250,000 award to a programme for detecting sepsis led by Federico Pallardó and José Luis García. August 5, 2013.
- News in El Médico Interactivo about the European E-IMD and E-HOD projects led by CIBERER. September 4, 2013.

CIBERER dissemination activities aimed at patients and society

The specific event in which CIBERER addresses patients and society as a whole together is undoubtedly the Rare Disease Day, entitled "Investigar es Avanzar". About 200 representatives from patient associations, companies and research groups attended the 2013 installment. Many other activities were organized to disclose the research conducted in CIBERER: events organized in collaboration with CIBERER units (see previous chapters), through social newsletters, etc.

Events and Other Activities

Events

In addition to those events and activities already mentioned in previous sections, such as the Translation Programme, and those expressly mentioned in the previous section, CIBERER has organized another series of highly relevant events on a national and international level, among which the following stands out:

- **International Symposium: "Mitochondrial diseases"**, organized by CIBERER and the Fundación Ramón Areces on May 20 and 21 in Madrid, coordinated by Dr. Rafael Garesse, Group Leader of CIBERER U717. Discussed topics were mitochondrial biology, molecular genetics of OXPHOS diseases, model systems for studying mitochondrial diseases or therapeutic approaches. Other investigators from various CIBERER units also participated in this event.
- **International Symposium: "Intellectual impairment: diagnostic challenges in the CgH array and next generation sequencing"**, organized by CIBERER and the Fundación Ramón Areces, on October 3 and 4 in Barcelona, coordinated by Dr. Montserrat Milà, Group Leader of CIBERER U726. Topics discussed included clinical and molecular aspects, advancements in diagnosis, early diagnosis and prevention, research, treatment and animal models in intellectual impairment.
- CIBERER organized the dissemination conference entitled **"Advanced therapies for the treatment of Rare Diseases"**, on October 25 in the Palacio Municipal de Congresos in Madrid. The latest progress made in the clinical application of advanced therapies was presented at this conference, including the approach to subjects such as gene therapy in adrenoleukodystrophy, immunodeficiencies, hepatic porphyrias, mucopolysaccharidosis, Fanconi anemia, epidermolysis bullosa and rare diseases in general. FEDER representatives also offered the patients' perspective on advanced therapies. This conference was held in the context of the joint Conference of the European and Spanish Gene and Cell Therapy Societies.
- Organization of the **Workshop «Research in genetic rare diseases. A social need»** at the local ONCE facilities in Valencia on November 25. Topics discussed included genetic and epidemiological research, and the opinion of the agents involved in the rare diseases about clinical research. The organizers of this Conference were Dr. Carmen Ayuso (U704) and Dr. José María Millán (U755).

Other Activities

- The documentary "Raras pero no invisibles" (Rare but not invisible), put together by the scientific dissemination production company from Malaga, Sombradoble, with funding obtained by means of crowdfunding, can be seen on the Internet free of charge. It lasts for one hour and was made with the collaboration of the following doctors at CIBERER: Francesc Palau, Lluís Montoliu, Pablo Lapunzina, Carmen Ayuso, José María Millán and Francisca Sánchez. Investigators working with and patients suffering from rare diseases offer their testimonies. The objective of the sponsors of "Raras pero no invisibles" is to make the Spanish population more sensitive to patients suffering rare diseases and to provide information about some of the research being conducted.

  https://www.youtube.com/watch?v= e4UwCIRhY&feature=youtu.be

- Investigators from the Universidad de Valencia published the report "Enfermedades minoritarias. Solos somos pocos, juntos somos muchísimos" (Rare Diseases: Alone there are just a few of us, united we are many), disseminating the concept, importance and characteristics of diseases with a low prevalence, in addition to the problems of living with one of these pathologies. Dr. Federico Pallardó, Group Leader of CIBERER U733, participated in preparing this report.

Service for handling queries by patients and professionals

CIBERER/Orphanet receives a large number of queries which we try to respond to provide guidance to patients in searching for the possible answers to the questions they are asking. To that end we have the immeasurable help of CIBERER investigators and clinicians and of the Orphanet Scientific Committee members as well as the FEDER Patient Information Service and Guidance, SIO.

The number of queries received in 2013 is the following:

Year	No. Queries by Patients	No. Queries by Professionals
2010	44	8
2011	84	27
2012	132	22
2013	130	23

As regards the type of RD, the origin or the receiving channel, the following types of queries were handled this year specifically:

- The queries made covered 120 different RD.
- Origin: 30% from Latin America; 65% from Spain and 5% from the rest of Europe.
- Receiving channel: 50% through Orphanet, the rest through consultas@, info@, telephone calls and known contacts.

As regards the help in resolving queries:

- 45% through Orphanet Scientific Committee members or through the Orphanet database.
- 50% with the help of CIBERER investigators, highlighting the participation of the following units: U753, U722, U724, U747, U714, U737, U703, U723, U704 and U755, among others.
- 5% with the collaboration of the SIO.

List of Publications

Overall, 2013 was the best year for CIBERER in terms of scientific production. The number of citable papers increased 16% in 2013 with respect to the year 2012, going from 9.61 to 10.45 per group (Figure 1). According to data available in April 2014, 676 CIBERER papers were published (Table 1 and Figure 2). If this figure, which virtually includes only citable documents, is combined with the meeting abstracts included in WoS there would be a total of 786 publications, 100 more than the previous year.

Table 1. CIBERER publications between 2006-2013

	Publications in the 2006 - 2013 period							
	2006	2007	2008	2009	2010	2011	2012	2013*
Article	203	327	388	322	397	461	426	488
Article; Book chapter	0	0	0	0	5	0	1	0
Article; Communication	13	17	13	4	1	3	1	0
Bibliographic element	0	0	2	0	0	0	0	0
Bibliographic notice	0	0	0	1	0	0	0	0
Correction	3	1	1	5	2	5	7	5
Editorial material	5	11	10	9	11	18	16	15
Letter	13	12	22	15	21	20	20	24
Abstract	73	126	69	139	111	118	167	110
Communication	0	0	2	1	0	3	4	1
Abstract	10	27	21	25	35	34	39	33
Abstract; Book chapter	0	0	0	0	1	0	2	0
All	320	521	528	521	584	662	683	676
Citable elements	239	383	446	367	460	521	493	546

**Provisional Results (April 2014)*

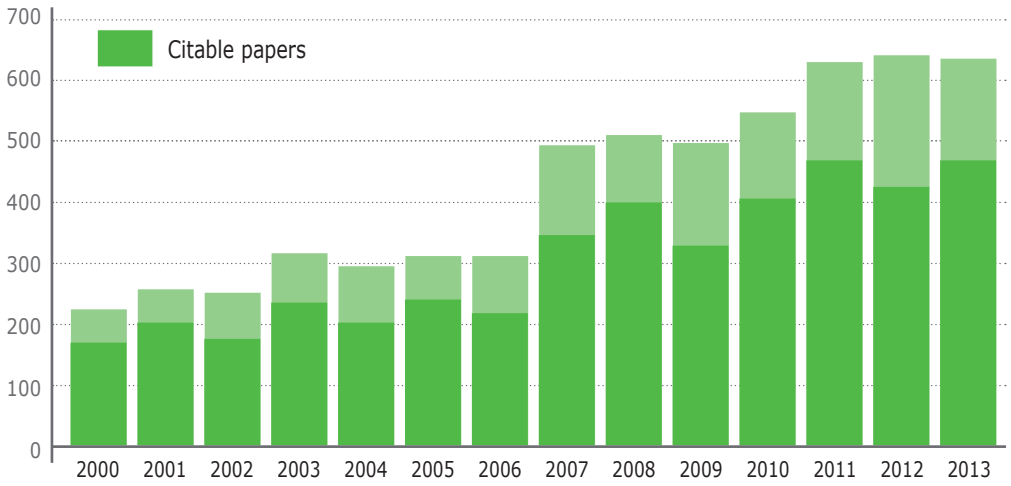
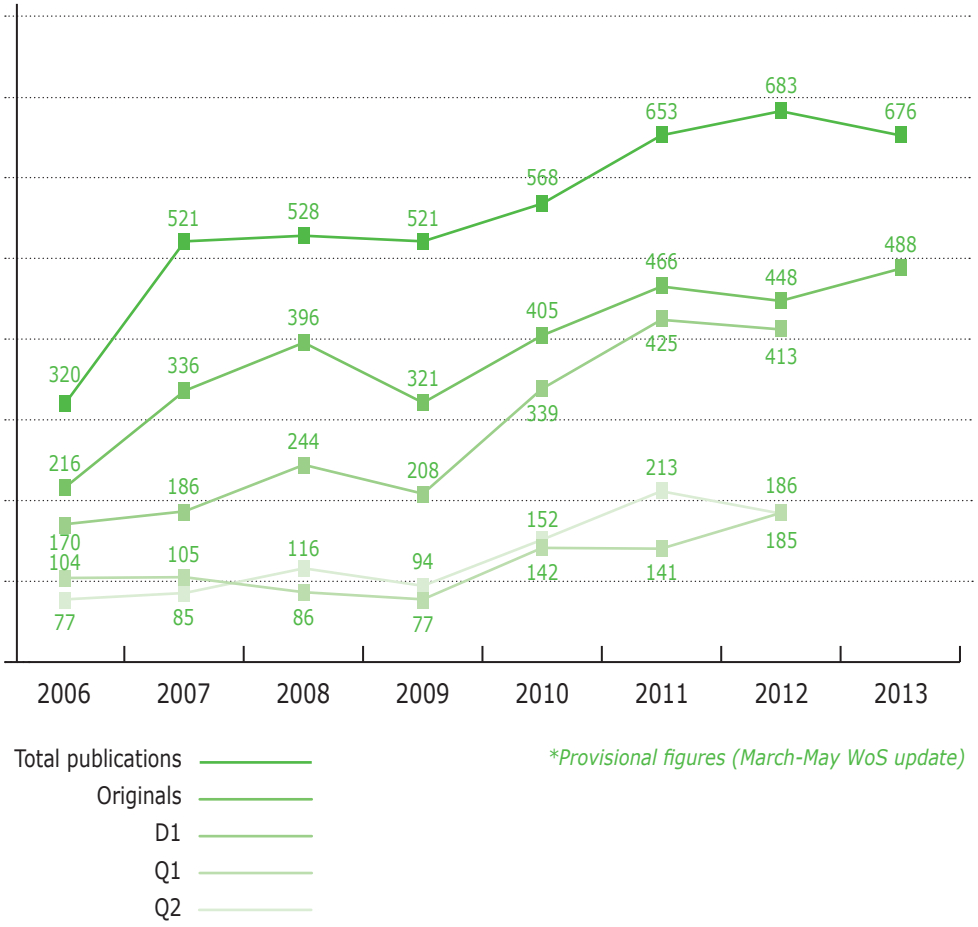


Figure 1. Evolution of the number of citable CIBERER papers (2000-2013)



**Provisional figures (March-May WoS update)*

Figure 2. Evolution of the number of CIBERER papers (2006-2013)* according to type

6 Research Groups

PROGRAMME:
Mitochondrial Medicine

Group U701

Group Members

STAFF MEMBERS

Cámara Navarro, Yolanda
Pinos Figueras, Tomás

ASSOCIATED MEMBERS

Andreu, Antoni L.
Carreño Gago, Lidia
Cuadros Arasa, Marc
García-Arumí, Elena
González Vioque, Emiliano
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Main lines of research

- Mechanisms of pathogenicity of mtDNA structural gene mutations.
- Genetic and biochemical study of mitochondrial DNA depletion syndromes: MNGIE, depletion due to TK2 or dGK deficiency and other. Implications in the control of the nucleotide pool.
- Therapeutic approaches for MNGIE and other mitochondrial DNA depletion syndromes.
- McArdle disease: study of pathomechanisms and potential therapeutic approaches.
- Characterization and study of the pathomechanisms involved in the limb-girdle muscular dystrophhy caused by mutations in the TNPO3 gene (LGMD1F).

Most relevant scientific articles

- Melià MJ, Kubota A, Ortolano S, Vílchez JJ, Gámez J, Tanji K, Bonilla E, Palenzuela L, Fernández-Cadenas I, Pristoupilová A, García-Arumí E, Andreu AL, Navarro C, Hirano M, Martí R. Limb-girdle muscular dystrophy 1F is caused by a microdeletion in the transportin 3 gene. Brain 2013;136:1508-17. IF (2012): 9.915, Decil 1 (Neurosciences).
- Cámara Y, González-Vioque E, Scarpelli M, Torres-Torronteras J, Martí R. Feeding the deoxyribonucleoside salvage pathway to rescue mitochondrial DNA. Drug Discov Today 2013;18:950-7. IF (2012): 6.551, Decil 1 (Pharmacology & Pharmacy).
- Pinós T, Melià MJ, Ortiz N, Martínez-Vea A, Raventós-Estellé A, Gallardo E, Hernández-Losa J, Cámara Y, Andreu AL, García-Arumí E. Identification of the novel mutation m.5658T>C in the mitochondrial tRNA(Asn) gene in a patient with myopathy, bilateral ptosis and ophthalmoparesis. Neuromuscul Disord 2013;23:330-6. IF (2012): 3.464, Cuartil 1 (Clinical Neurology).
- Blanco-Grau A, Bonaventura-Ibars I, Coll-Cantí J, Melià MJ, Martínez R, Martínez-Gallo M, Andreu AL, Pinós T, García-Arumí E. Identification and biochemical characterization of the novel mutation m.8839G>C in the mitochondrial ATP6 gene associated with NARP syndrome. Genes Brain Behav 2013;12:812-20. IF (2012): 3.597, Cuartil 1 (Behavioral sciences).
- Perier C, Bender A, García-Arumí E, Melià MJ, Bové J, Laub C, Klopstock T, Elstner M, Mounsey RB, Teismann P, Prolla T, Andreu AL, Vila M. Accumulation of mitochondrial DNA deletions within dopaminergic neurons triggers neuroprotective mechanisms. Brain 2013;136:2369-78. IF (2012): 9.915, Decil 1 (Neurosciences).

Highlights

- We found the gene (TNPO3) whose mutations cause a form of dominant limb girdle muscular dystrophy (LGMD1F) discovered and characterized genetically by our group some time ago (Melià et al, Brain 2013). This represents a significant progress in the field of muscular dystrophies and opens interesting possibilities for synergy, as transportin 3 (encoded by TNPO3) participates in the process of HIV infection, and is currently a hot topic in this area. In fact, we have already started a very productive collaboration with other researchers working on HIV infection.
- We have initiated the development of EUROMAC, a European project funded by DG- SANCO (Directorate General for Health & Consumers, European Commission), of which we are the coordinator group. EUROMAC has 20 partners from 8 European countries and the U.S., and its main objective is to create an international registry of patients with McArdle's disease or other glycogenoses. In addition to developing its specific objectives, this project has helped us to expand our international collaborations and to increase our knowledge on the important field of rare disease registries.

Besides these two major milestones, during 2013 we have also significantly progressed in the field of conventional and advanced therapies (gene therapy) for mitochondrial DNA depletion syndromes, resulting in a publication in 2013 (Cámara et al, Drug Discov Today, 2013) and two recently published papers (Cámara et al, Hum Mol Genet 2014; Torres-Torronteras et al, Mol Ther 2014) . We have also contributed to expand the knowledge of disorders caused by primary mutations in mitochondrial DNA, with the description and characterization of two novel pathogenic mutations (Pinós et al, Neuromuscul Disord 2013; Blanco-Grau et al, Genes Brain Behav 2013).

PROGRAMME:
Genetic Medicine

Group U702

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Main lines of research

- Hereditary retinal dystrophies.
- Enteric nervous system disorders. Hirschsprung's disease and neuronal intestinal dysplasia.
- Genetics of thyroid cancer.
- Intellectual disability.
- Breast and/or ovarian cancer.
- Colon cancer.
- Spinal muscular atrophy.
- Cell therapy.
- Fetal therapy.
- Application of NGS in the discovery of new genes in rare diseases.
- Development of tools for predicting pathology penetrance and expression
- Genomic approaches for the diagnosis of rare diseases.

Most relevant scientific articles

- Pathways systematically associated to Hirschsprung's disease. Fernández RM, Bleda M, Luzón-Toro B, García-Alonso L, Arnold S, Sribudiani Y, Besmond C, Lantieri F, Doan B, Ceccherini I, Lyonnet S, Hofstra RM, Chakravarti A, Antiñolo G, Dopazo J, Borrego S. Orphanet J Rare Dis. 2013 Dec 2;8:187. doi: 10.1186/1750-1172-8-187.
- DNA copy number profiling reveals extensive genomic loss in hereditary BRCA1 and BRCA2 ovarian carcinomas. Kamieniak MM, Muñoz-Repeto I, Rico D, Osorio A, Urioste M, García-Donas J, Hernando S, Robles-Díaz L, Ramón Y Cajal T, Cazorla A, Sáez R, García-Bueno JM, Domingo S, Borrego S, Palacios J, van de Wiel MA, Ylstra B, Benítez J, García MJ. Br J Cancer. 2013 Apr 30;108(8):1732-42. doi: 10.1038/bjc.2013.141.
- Chromosome 21 scan in Down syndrome reveals DSCAM as a predisposing locus in Hirschsprung disease. Jannot AS, Pelet A, Henrion-Caude A, Chaoui A, Masse-Morel M, Arnold S, Sanlaville D, Ceccherini I, Borrego S, Hofstra RM, Munnich A, Bondurand N, Chakravarti A, Clerget-Darpoux F, Amiel J, Lyonnet S. PLoS One. 2013 May 6;8(5):e62519. doi: 10.1371/journal.pone.0062519.
- Mutational spectrum of semaphorin 3A and semaphorin 3D genes in Spanish Hirschsprung patients. Luzón-Toro B, Fernández RM, Torroglosa A, de Agustín JC, Méndez-Vidal C, Segura DI, Antiñolo G, Borrego S. PLoS One. 2013;8(1):e54800. doi: 10.1371/journal.pone.0054800. Epub 2013 Jan 23.
- Contributions of PHOX2B in the pathogenesis of Hirschsprung disease. Fernández RM, Mathieu Y, Luzón-Toro B, Núñez-Torres R, González-Meneses A, Antiñolo G, Amiel J, Borrego S. PLoS One. 2013;8(1):e54043. doi: 10.1371/journal.pone.0054043.

Highlights

The activity of our group in 2013 is reflected in 19 scientific publications, accumulating an average impact factor of 3.24.

We have received competitive external research funding for 7 different projects, (CTS-03687, PI10/01290, PI-0154/2010, PI11/02923, CTS-7447, CIVP16A1856, PI-0105-2011), one of them belonging to the Intrasalud program. We highlight that two of these grants are in collaboration with the CIBERER group of Dr. Dopazo. Also, our group has been funded by "Acciones Cooperativas y Complementarias Intramurales Raras" in collaboration with other CIBERER groups (Dra. Ayuso, Dr. Millán y Dr. Dopazo).

It is worth mentioning the agreement of Dr. Antiñolo as Scientific Director of "Acción Multidisciplinar en Enfermedades Raras y Medicina Personalizada" funded by CDTI-FEDER interconnecta (EXP000528 87/ITC-20111037).

In the context of international and national cooperative activities, our group has published 2 articles in collaboration with the International Consortium of Hirschsprung disease (HSCR), of which we are part together with Dr. Hofstra (Netherlands), Dr. Lyonnet (France), Dr. Chakravarti (USA), Dr. Ceccherini (Italy) and Dr. Tam (Hong Kong), as well as 4 publications with Dr. Benitez, Dr. Dopazo and Dr. Robledo.

In addition, we have demonstrated the utility of next-generation sequencing for the diagnosis of genetically heterogeneous disorders such as Inherited Retinal Dystrophies (IRD) and hereditary breast and ovarian cancer. The application of this approach has significantly increased the performance of the genetic diagnosis in our cohort. Besides, we are also implementing this tool for the diagnosis of Hirschsprung Disease. Likewise, we are developing a method of whole genome amplification for preimplantation genetic diagnosis.

Finally, during the year 2013, we have contributed to the development of a database including all germline sequence variants in Spanish patients in collaboration with Dr. Lapunzina, Dr. Tizzano, Dr. Millan, Dr. Carracedo and Dr. Ayuso.

PROGRAMME:
Inherited Metabolic Medicine

Group U703

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Main lines of research

- Intermediary metabolism congenital errors (amino acid disorders and organic acidurias)
- Mitochondrial oxidative phosphorylation defects. Primary coenzyme Q10 deficiency.
- Neurometabolic diseases: Inborn errors of dopamine and serotonin biosynthesis, of glucose and folate transport through blood brain barrier. Cerebral creatine deficiency syndromes.
- Treatment with orphan drugs for several genetic diseases. Clinical and biochemical follow-up of patients.
- Congenital muscle distrophies

Most relevant scientific articles

- Pons R, Syrengelas D, Youroukos S, Orfanou I, Dinopoulos A, Cormand B, Ormazabal A, Garzía-Cazorla A, Serrano M, Artuch R. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord. 2013 Jul;28(8):1058-63.
- Molero-Luis M, Serrano M, Ormazábal A, Pérez-Dueñas B, García-Cazorla A, Pons R, Artuch R Homovanillic acid in cerebrospinal fluid of 1388 children with neurological disorders. Neurotransmitter Working Group. Dev Med Child Neurol. 2013 Jun;55(6):559-66.
- Reversible lactic acidosis in a newborn with thiamine transporter-2 deficiency. Pérez-Dueñas B, Serrano M, Rebollo M, Muchart J, Gargallo E, Dupuits C, Artuch R. Pediatrics. 2013 May;131(5):e1670-5.
- Protein expression profiles in patients carrying NFU1 mutations. Contribution to the pathophysiology of the disease. Ferrer-Cortès X, Font A, Bujan N, Navarro-Sastre A, Matalonga L, Arranz JA, Riudor E, del Toro M,García-Cazorla A, Campistol J, Briones P, Ribes A, Tort F. J Inherit Metab Dis. 2013 Sep;36(5):841-7.
- Coenzyme Q10 deficiency in mitochondrial DNA depletion syndromes. Montero R, Grazina M, López-Gallardo E, Montoya J, Briones P, Navarro-Sastre A, Land JM, Hargreaves IP, Artuch R; Coenzyme Q10 Deficiency Study Group. Mitochondrion. 2013 Jul;13(4):337-41.

Highlights

During 2013, we are developing several research projects funded by public and private institutions. Nine of them are highlighted, since it has been funded by the Instituto de Salud Carlos III (6) and by the European Union (3). The topics related with these projects are neurometabolic diseases of neurotransmission and vitamins, and mitochondrial disorders caused by Coenzyme Q10 deficiency. Regarding our main milestones, we have participated with other CIBERER groups in the description of new genes associated with metabolic diseases. During 2013, we have published 30 papers in international scientific journal indexed in PubMed, most of them in the 1st and 2nd quartiles according to ISI Web of Knowledge. We are involved in several clinical trials, which details are available on request (www.fsjd.org). Concerning clinical guides and translational activities to society, we have developed the web page www.guíametabolica.org, with more than 600.000 visits, and 2000 registered users worldwide. In this webpage, scientific and general contents about 55 metabolic diseases are loaded, and we also offer an on-line consult-service for patients at the national and international level. Our researches are actively participating in several scientific and familial associations in Spain and foreign countries related with rare diseases. As a fact of paramount importance, during September 2013, our group together with the "Instituto de Bioquímica Clínica de Barcelona", organized the international congress of inborn errors of metabolism (www.ICIEM.org) in Barcelona, with around 2500 participants. Details of this meeting are available in the SSIEM website.

PROGRAMME:
Sensorineural Pathology

Group U704

Group Members

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Main lines of research

- Hereditary retinal dystrophies: identification of new genes and mutational mechanisms, genotype–phenotype correlation, genetic epidemiology, modifying genetic factors and development of algorithms.
- Complex neurodegenerative diseases: omic approach models.
- Pharmacogenetics.
- Quality control over genetic and genomic studies. Ethical aspects and informed consent.
- Infertility: Genetic and chromosomal factors.
- Non-invasive prenatal diagnosis applied to Mendelian and aneuploidy disorders.
- Genetic cardiovascular diseases: sudden death and cardiomyopathy.
- Ocular malformations, aniridia, anophthalmia, glaucoma and others.
- Neuromuscular and neurological diseases.
- Congenital skeletal abnormalities.

Most relevant scientific articles

- Gómez Tortosa E, Gallego J, Guerrero López R, Marcos A, Gil Neciga E, Sainz MJ, Díaz A, Franco Macías E, Trujillo Tiebas MJ, Ayuso C, Pérez Pérez J. C9ORF72 hexanucleotide expansions of 20 22 repeats are associated with frontotemporal deterioration. Neurology. 2013 Jan 22;80(4):366 70. PMID: 23284068. IF(2012): 8,249 5 Year Impact Factor (2012): 8,397 Q(2012) Q1 D1 (8:191). ISSN: 1526 632X.
- Riveiro Alvarez R, López Martínez MA, Zernant J, Aguirre Lamban J, Cantalapiedra D, Avila Fernández A, Gimenez A, López Molina MI, García Sandoval B, Blanco Kelly F, Corton M, Tatu S, Fernández San José P, Trujillo Tiebas MJ, Ramos C, Allikmets R, Ayuso C. Outcome of ABCA4 disease associated alleles in autosomal recessive Retinal Dystrophies: Retrospective analysis in 420 Spanish families.Ophthalmology. 2013 Nov;120(11):2332 7 PMID: 23755871. IF(2012): 5,563 5 Year Impact Factor (2012): 5,777 Q(2012) Q1 D1 (2:58).
- Manes G, Meunier I, Avila Fernández A, Banfi S, Le Meur G, Zanlonghi X, Corton M, Simonelli F, Brabet P, Labesse G, Audo I, Mohand Said S, Zeitz C, Sahel JA, Weber M, Dollfus H, Dhaenens CM, Allorge D, de Baere E, Koenekoop RK, Kohl S, Cremers FP, Hollyfield JG, Sénéchal A, Hebrard M, Bocquet B, Ayuso García C, Hamel CP. Mutations in IMPG1 cause vitelliform macular dystrophies. Am J Hum Genet. 2013 Sep 5;93(3):571 8. doi: 10.1016/j.ajhg.2013.07.018. Epub 2013 Aug 29. PMID: 23993198 IF(2012): 11,202 5 Year Impact Factor (2012): 12,512 Q(2012) Q1 D1 (7:161).
- Cortón M, Nishiguchi KM, Ávila Fernández A, Nikopoulos K, Riveiro Alvarez R, Tatu SD, Ayuso C, Rivolta C. Exome sequencing of index patients with retinal dystrophies as a tool for molecular diagnosis. PLoS One. 2013 Jun 14;8(6):e65574. PMID: 23940504 IF(2012): 3,730 5 Year Impact Factor (2012): 4,244 Q(2012) Q1 (7:56).
- Corton M, Tatu SD, Avila Fernández A, Vallespín E, Tapias I, Cantalapiedra D, Blanco Kelly F, Riveiro Alvarez R, Bernal S, García Sandoval B, Baiget M, Ayuso C. High frequency of CRB1 mutations as cause of Early Onset Retinal Dystrophies in the Spanish population. Orphanet J Rare Dis. 2013 Feb 5;8:20 PMID: 23379534. IF(2012): 4,315 5 Year Impact Factor (2012): 5,715 Q(2012) Q1 (26:121).

Highlights

22 scientific articles (cumulative IF : 82.455) and 2 chapters in the book "Luces y sombras en la investigación médica" and contribution to the development of two clinical guidelines:

- "Secuenciación genómica en la práctica clínica. Documento de conclusiones".
- "Proyecto de Orden por la que se concreta y actualiza la cartera común básica de Servicios asistenciales del Sistema Nacional de Salud. Noviembre de 2013".

12 funded projects (4 public projects, 6 private projects, 1 European project and 1 CIBERER intramural ACCI project). During 2013 we applied to 6 competitive calls for funding research projects:

- 2 obtained project: 1 "Sara Borrell" Contract and 1 "health research AES 2013" (PI13/00226).
- 4 resolution pending projects: 3 private and 1 of the Community of Madrid.

Participation in EyeTN Initial Training Network (ITN): European Commission

Marie Curie Initial Training Networks (ITN) (Call: FP7-PEOPLE-2012-ITN)

Participation in Phase II Multicenter EECC (No. EUDRACT: 2011-004349-42) in Fragile X Syndrome.

As a result of the research we have identified one new gene responsible for ER (in press) and 4 new genotype-phenotype associations (ABHD12 (PMID: 24697911) and 3 to be published) and 7 new diagnoses added (Lasik Corneal Dystrophy, methylmalonic aciduria, Charge Syndrome and 4 biomarkers predictive of drug response : CYP2C9 , CYP2C19 , CYP2D6 and CES1).

HR 3 hired CIBERER (1 and 2 postdoctoral laboratory technicians), 1 PhD student Rio Hortega (CM12/00013), 1 Sara Borrell (CD12/00676), 1 Technical Support Research (CA12/00296), 1 Miguel Servet (CP12/03256) and a contract ISCIII intensified.

Participation in teaching activities for undergraduate (8 in Medicine School, Science and Nursing in UAM and 4 trainees), postgraduate (master classes at 17 and 2 trainees) and 11 postgraduate courses. The U704 also has organized 7 National and International Meetings on Translational Research and Personalized Medicine, Pharmacogenetics, Research and Therapies in RD.

PROGRAMME:
Genetic Medicine

Group U705

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Main lines of research

- Study of clinical-genetic heterogeneity of limb-girdle muscular dystrophies exhibiting autosomal recessive transmission and autosomal dominant transmission.
- Mutational and expression study in the dysferlin gene: association with three different phenotypes: C63 Miyoshi's myopathy and distal anterior myopathy.
- Studies of molecular pathology, mechanisms of disease, SMN gene expression and the expression of possible modifying genes in spinal muscular atrophy.
- Development of iPSCs in patients with spinal muscular atrophy as a neuronal model of study of the disease.
- Study of spinal muscular atrophy as a human developmental disease.
- Hereditary breast cancer.
- Identification and characterization of circulating tumor cells (CTCs) in patients with breast cancer: identification of a prognostic gene expression profile.
- Pharmacogenetics: Adverse drug reactions.
- Congenital coagulopathies: molecular pathology of hemophilia and von Willebrand disease.
- Elaboration of molecular diagnostic panels in hereditary monogenic pathology by means of the nanofluid system and massive sequencing.

Most relevant scientific articles

- Martínez-Hernández R, Bernal S, Also-Rallo E, Alías L, Barceló MJ, Hereu M, Esquerda JE, Tizzano EF. Synaptic defects in type I spinal muscular atrophy in human development. The Journal of Pathology 2013. Jan;229(1):49-61. doi: 10.1002/path.4080.
- Domingo P, Cabeza Mdel C, Torres F, Salazar J, Gutierrez Mdel M, Mateo MG, Martínez E, Domingo JC, Fernández I, Villarroya F, Ribera E, Vidal F, Baiget M. Association of thymidylate synthase polymorphisms with acute pancreatitis and/or peripheral neuropathy in HIV-infected patients on stavudine-based therapy. PLoS One. 2013;8(2):e57347. doi: 10.1371/journal.pone.0057347.
- Juan-Mateu J, González-Quereda L, Rodríguez MJ, Verdura E, Lázaro K, Jou C, Nascimento A, Jiménez-Mallebrera C, Colomer J, Monges S, Lubieniecki F, Foncuberta ME, Pascual-Pascual SI, Molano J, Baiget M, Gallano P. Interplay between DMD point mutations and splicing signals in Dystrophinopathy phenotypes. PLoS One. 2013;8(3):e59916. doi: 10.1371/journal.pone.0059916.
- Sebio A, Páez D, Salazar J, Berenguer-Llergo A, Paré-Brunet L, Lasa A, Del Río E, Tobeña M, Martín-Richard M, Baiget M, Barnadas A. Intergenic polymorphisms in the amphiregulin gene region as biomarkers in metastatic colorectal cancer patients treated with anti-EGFR plus irinotecan. Pharmacogenomics J. 2013 Aug 20. doi: 10.1038/tpj.2013.29.
- Corton M, Tatu SD, Avila-Fernández A, Vallespín E, Tapias I, Cantalapiedra D, Blanco-Kelly F, Riveiro-Alvarez R, Bernal S, García-Sandoval B, Baiget M, Ayuso C. High frequency of CRB1 mutations as cause of Early-Onset Retinal Dystrophies in the Spanish population. Orphanet J Rare Dis. 2013 Feb 5;8:20.

Highlights

The U705 has wide experience and knowledge in the research and diagnosis of rare diseases, with consolidated research lines in the fields of neuromuscular and haematological diseases, Pharmacogenetics and Oncogenetics. The most important activities of the group in 2013 are highlighted below.

The Unit has received national and international funding for research projects (from FIS/ISCIII, the MICINN and MINCYT). As a result of this funding, the unit is developing gene panels in order to implement the new NGS technology into clinical practice. Additionally, the unit contributes to the Human Variome Project with the study "Development of a national database of mutations in germinal lines".

The results of these studies have yielded 15 scientific articles, 80% were in the first decil or first quartile publications.

Regarding translational research, the Unit is conducting a clinical trial in Pharmacogenetics funded by the FIS/ISCIII and is participating in an international clinical trial in nmDBMD funded by PTC Therapeutics. The Unit also participates in international organisations such as the DMD Registry (TREAT-NMD) and the Registry of SMN patients, and collaborates with scientific societies and patient associations (ASEM and SEN).

Regarding knowledge transfer and patents, the Unit has signed two contracts with private entities (Gebro Pharma S.A. and Sistemas Genómicos, S.L.) in the field of Pharmacogenetics.

The Unit has a recognized expertise in the training of researchers and PhD students, and has incorporated new clinical research fellows funded by the prestigious studentships Río Ortega.

The Unit coordinates the first postgraduate course in Clinical Pharmacogenetics and Pharmacogenomics (IL3 -UB) at national level.

The Unit has organized a national meeting for AME researchers in the Hospital Sant Pau, in May 2013.

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U706

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Main lines of research

- Hereditary breast cáncer.
- Cromosomal instability síndrome.
- Genetic Epidemiology.
- Cromosomal alterations.
- Hereditary colorectal cáncer.
- Familial endocrine cáncer.
- Pharmacogenetics and cáncer.
- Hereditary ovarian cáncer.

Most relevant scientific articles

- Michailidou K, P. Hall et al. A. Dunning, J. Benitez, D. Easton (2013). Large scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 45, 353-361.
- Comino-Méndez I, et. Al. (2013). Tumoral EPAS1 (HIF2A) mutations explain sporadic pheochromocytoma and paraganglioma in the absence of erythrocytosis. Hum Mol Genet 22, 2169-2176.
- de Cubas AA, et al. (2013). Integrative analysis of miRNA and mRNA expression profiles in pheochromocytoma and paraganglioma identifies genotype-specific markers and potentially regulated pathways. Endocr-Relat Cancer 20, 477-493.
- Gracia-Aznares FJ, Fernández V et al. Devilee P, Benitez J. (2013) Whole exome sequencing suggest much of non BRCA1/2 breast cancer is due to moderate and low susceptibility allele. Plos One 8(2):e55681.
- Osorio A, Bogliolo M, et al. , Surrallés J, Benítez J (2013). Evaluation of rare variants in the new fanconi anemia gene ERCC4 (FANCQ) as familial breast/ovarian cancer susceptibility alleles. Hum Mutat 34(12):1615-8.

Highlights

U706 works in the study of genetic bases of familial cancer. The main activity is focused in the study of breast and ovarian cancer, colorectal cancer and endocrine tumors.

In the first case we want to remark the group of papers that were published in April, in a Nature monography (Nature Collections iCOGS, April 2013) that includes 9 Nat Genet and 2 Nat Communicat identifying new susceptibility genes to breast and ovarian cancer. These genes also explain a percentage of familial cancer risk. These works belong to the results obtained in the iCOGS European project in which J.Benitez was the coordinator of a working group and also the coordinator of one of the main papers (Michailidou K et al, Nat Genet 2013).

In colorectal cancer we want to remark the association of a new gene AXIX2 with a specific moderated subtype of polyposis colorectal cancer (APC).

With regard to endocrine cancer, genetic heterogeneity is one of the main characteristics and every year a new gene is discovered. In this occasion our group has demonstrated the relation between the new EPAS1 gene and pheochromocitoma/paraganglioma tumors. Somatic mutations induce hypoxia that deregulate some genes important for cancer development. (Comino-Mendez I et al. . Hum Mol Genet 2013)

Finally is important to consider the work that we are doing in the search for new high susceptibility genesto families with rare and /or infrequent cancers by whole exome sequencing. This work started in 2010 and we are obtaining very good results that we are starting to publish (Gracia Aznares FJ et al, Plos One 2013).

PROGRAMME:
Genetic Medicine

Group U707

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Main lines of research

- Studies of expression, function and structure of endoglin and ALK1 and their relevance in hereditary hemorrhagic telangiectasia and other pathologies such as preeclampsia.
- Genetic and cellular studies on the Spanish population with hereditary hemorrhagic telangiectasia.
- Molecular diagnostics and characterization of pathogenic mechanisms of hereditary hemorrhagic telangiectasia in the TGF-beta signaling pathway.
- Cellular and animal models for studying the function of endoglin and ALK1 in physiopathology

Most relevant scientific articles

- Garrido-Martín EM, Blanco FJ, Roqué M, Novensá L, Tarocchi M, Lee UE, Suzuki T, Friedman SL, Botella LM, Bernabéu C. Vascular injury triggers Kruppel-like factor 6 (KLF6) mobilization and cooperation with Sp1 to promote endothelial activation through upregulation of the Activin Receptor-Like Kinase 1 (ALK1) gene. Circ. Res. (2013) 112: 113-127.
- Rossi E, Sanz-Rodríguez F, Eleno N, Düwell A, Blanco FJ, Langa C, Botella LM, Cabañas C, López-Novoa JM, Bernabeu C. Endothelial endoglin is involved in inflammation: role in leukocyte adhesion and transmigration. Blood. (2013) 121: 403-415.
- Tabruyn SP, Hansen S, Ojeda-Fernández ML, Bovy N, Zarrabeitia R, Recio-Poveda L, Bernabéu C, Martial JA, Botella LM, Struman I. MiR-205 is downregulated in hereditary hemorrhagic telangiectasia and impairs TGF-beta signaling pathways in endothelial cells. Angiogenesis. (2013) 16(4): 877-887.
- Wooderchak-Donahue WL, McDonald J, O'Fallon B, Upton PD, Li W, Roman BL, Young S, Plant P, Fülöp GT, Langa C, Morrell NW, Botella LM, Bernabeu C, Stevenson DA, Runo JR, Bayrak-Toydemir P. BMP9 Mutations Cause a Vascular-Anomaly Syndrome with Phenotypic Overlap with Hereditary Hemorrhagic Telangiectasia. Am. J. Hum. Genet. (2013) 93(3): 530-537.
- Fontalba A, Fernández-Luna JL, Zarrabeitia R, Recio-Poveda L, Albiñana V, Ojeda-Fernández ML, Bernabeu C, Alcaraz LA, Botella LM. Copy number variations in endoglin locus: mapping of large deletions in Spanish families with hereditary hemorrhagic telangiectasia type 1. BMC Med. Genet. (2013) Nov 25; 14(1):121.

Highlights

This unit coordinates several studies at the basic, clinical and translational levels on Hereditary Hemorrhagic Telangiectasia (HHT). HHT is caused by mutations in endoglin and ALK1 genes. These activities have been funded mainly by two current research projects of the Spanish National Plan (SAF2010-19222 y SAF2011-23475), as well as by intramural funding from CIBERER. The research activity on the molecular basis of HHT has allowed us to describe new mutations with large deletions in the endoglin gene, as well as to demonstrate for the first time that mutations in the BMP9 gene lead to an HHT-like syndrome. We have also reported a new function for endoglin in cell adhesion as an integrin ligand. Regarding the clinic, as a reference group for HHT in Spain, we have carried out screening protocols, molecular diagnosis, genetic counseling and pharmacological and interventional therapies. We have coordinated a meeting in Zaragoza with a large number of clinicians, which has allowed the creation of the first national network for HHT. We have collaborated with different national and international patients associations for rare diseases, including FEDER and we have contributed with an active involvement in the organization of the 10th International Hereditary Hemorrhagic Telangiectasia Scientific Conference (Cork, Irlanda). With respect to the translational activity, and upon reaching the designation for Raloxifene as the first orphan drug in HHT, we have carried out studies with Bazedoxifene in HHT postmenopausic women with the goal of getting a new designation as orphan drug for HHT. Regarding the technology transfer item, we have applied for an international PCT patent on an inhibitor of soluble endoglin and its potential use in pathologies such as preeclampsia, where soluble endoglin has a pathogenic effect.

PROGRAMME:
Endocrine Medicine

Group U708

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Main lines of research

- CONGENITAL HYPOTHYRODISM: Mechanisms of action of the thyroid hormone in the brain. Physiopathology of neural alterations over thyroid hormone deprivation during the fetal and neonatal periods. Influence of maternal thyroid hormones and consequences of maternal hypotiroxinemia over gene expression in the fetal brain.
- SLC16A2 MUTATIONS: Physiopathology of the Allan-Herndon-Dudley syndrome and deficiency of T3 transport in the syndrome using transporter knock out mice. Development of new therapeutic approaches based on thyroid hormone analogues with alternative transport.
- THYROID HORMONE RESISTANCE: alteration mechanisms in mental retardation and attention deficit- hyperactivity disorder as a consequence of beta type T3 receptor mutations.

Most relevant scientific articles

- Gil-Ibañez P, Morte B, Bernal J. Role of Thyroid Hormone Receptor Subtypes α and β on Gene Expression in the Cerebral Cortex and Striatum of Postnatal Mice. Endocrinology 154: 1940-1947, 2013.
- Ferrara AM, Liao XH, Gil-Ibáñez P, Marcinkowski T, Bernal J, Weiss RE, Dumitrescu AM, Refetoff S. Changes in thyroid status during perinatal development of MCT8-deficient male mice. Endocrinology. 154:2533-41, 2013.
- Bernal J, Morte B. Thyroid hormone receptor activity in the absence of ligand: Physiological and developmental implications. Biochim Biophys Acta. 1830: 3893-3899, 2013.
- Rodrigues, T.B., Ceballos, A., Grijota-Martínez, C. Núñez, B., Refetoff, S., Cerdán, S., Morte, B., Bernal, J.: Increased oxidative metabolism and neurotransmitter cycling in the brain of mice lacking the thyroid hormone transporter Slc16a2 (Mct8). PLOS One 8(10): e74621, 2013.
- D. Navarro, M. Alvarado, B. Morte, D. Berbel, J. Sesma, P. Pacheco, G. Morreale de Escobar, J. Bernal and P. Berbel. Late maternal hypothyroidism alters the expression of Camk4 in neocortical subplate neurons. A comparison with Nurr1 labeling. Cerebral Cortex, 2013 May 24. [Epub ahead of print].

Highlights

Our group has participated in the E-RARE 2013 call together with groups from Germany and Israel with the project "ALLAN-HERNDON-DUDLEY SYNDROME: MECHANISMS OF DISEASE AND THERAPEUTIC APPROACHES IN MODEL ORGANISMS" which was finally selected to be financed for three years between June 2014 to June 2017. Among the projects we have also to remark one from the Mehuer Foundation on Orphan Drugs and Rare Diseases entitled "PRECLINICAL STUDIES ON THE EFECTIVENESS OF THE THYROID HORMONE ANALOG TRIAC AS A TREATMENT OF ALLAN-HERNDON-DUDLEY SYNDROME". Among the more relevant results from our group are those related to the study of the pathology of Allan-Herndon-Dudley syndrome, in collaboration with groups from Chicago, Israel and Australia. In this study we analyzed brain samples from necropsies, and is the first study on the pathology of the syndrome. We describe specific structural alterations of the cerebral cortex and cerebellum in a 30-week fetus and an 11 year old child.

We have continued to distribute our clinical guide to diagnose the syndrome, for example qith a seminar at the Sant Joan de Deu, Barcelona, which permitted the diagnosis of additional cases in our country. Among the invited lectures, we select those given in meetings organized by affected families in Los Angeles, USA, on January 2013 and again in 2014, the opening lecture on Resistance to Thyroid Hormones, a course organized by the Spanish Society of Endocrinology and Lilly laboratories, November 2013. Samuel Refetoff, Professor of the University of Chicago spent a 15 day stay in our lab under the Fulbright Professor program. During his visit, we organized with the collaboration of the CIBERER a clinical session at the Hospital La Paz.

PROGRAMME:
Sensorineural Pathology

Group U709

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Main lines of research

- Determination of the transcriptional network regulating ocular development and its implication in congenital developmental disorders.
- Study of the molecular basis for hereditary retinal dystrophies and generation of animal models.
- Study of the function of the Shh and Wnt signaling pathways in axon guidance and its implications in congenital visual system disorders.
- Regulation of metalloprotease activity in nervous system development and its implications in congenital developmental disorders and cell homeostasis.
- Study of the physiopathological basis for Lafora disease.

Most relevant scientific articles

- Beccari L., Marco-Ferreres, R and Bovolenta P. (2013) The logic of Gene Regulatory Networks in early vertebrate forebrain patterning. Mech. Dev. 130, 95-111. (cover caption article).
- Indrieri, A., Conte, I., Chesi, GC, Quartararo, J., Cermola M, Tate, R., Ghezzi, D., Zeviani M, Goffrini, P., Ferrero, I., Bovolenta, P., and Franco, B. (2013) The impairment of HCCS leads to MLS syndrome by activating a non-canonical cell death pathway in the brain and eyes. EMBO Mol Med. 5, 280–293. (cover caption article).
- Ferri A., Favaro R.*, Beccari L*, Bertolini J., Tosetti V., Verzeroli C., Nieto-López, F., Mercurio S., La Regina, F., Ottolenghi S., Bovolenta P. and Nicolis, S.K. (2013) Sox2 is required for embryonic development of the ventral telencephalon through the activation of the ventral determinants Nkx2.1 and Shh. Development 140, 1250-1261. *Equally contributing.
- Conte I. Banfi S and Bovolenta P. (2013) Noncoding RNAs in the development of sensory organs and related diseases. Cell. Mol. Life Sci. 70:4141–415.
- Sanchez-Arrones, L.*, Nieto-López, F.*, Sanchez-Camacho, C., Carreres M.I., Herrera, E., Okada, A. and Bovolenta, P. (2013) Shh/Boc signaling is required for sustained generation of ipsilateral-projecting ganglion cells in the mouse retina. J. Neurosci. 33, 8596-8607. (Featured article). *Equally contributing.

Highlights

During this year the team has progressed significantly in elucidating the molecular mechanisms underlying known congenital eye diseases as well as towards the identification of the gene regulatory networks underlying eye development in vertebrates, a consolidated approach that is continuously leading to the identification of additional candidates gene for microphthalmia, anopthalmia and coloboma.

The work of the team was supported by national and international grants and was presented in eight international congresses with a total of ten communications. The most relevant are invited presentations at the following conferences: 1) Signaling in vertebrate hedgehog and Gli signaling in stem cells and cancer. Fondation des Treilles, France 15-20 April. 2) British Society for Developmental Biology (BSDB). Axon guidance and Regeneration. 28-30 August. Aberdeen University, Scotland, UK. 3) International Mammalian Genome Society. September 16-18. Salamanca (pleanary conference). 4) 2nd Meeting Portuguese Society for Developmental Biology (SPBD) 24-26 October. The team was also involved in the organization of the very successful 8th European Zebrafish meeting in Barcelona.

Different members of the unit has been involved in teaching and outreach activities, including the delivery of seminars in national and international research centres, the participation in the Developmental Neurobiology Course of the Master in Neuroscience UAM-Instituto Cajal; the Development course of the Master in Molecular Biology of the UAM and the 2nd International course "From Pigment Cell Development to Melanomas" Institut Curie/CNRS. Marco Cardozo has successfully (Magna Cum Laude) defended his doctoral thesis titled "The Shh binding protein Cdon is required for patterning and morphogenesis of the vertebrate eye". Facultad de Ciencias, Universidad Autónoma de Madrid.

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U710

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Main lines of research

- Cell and gene therapy for rare diseases.
- Stem cell research and applications.
- Research of the molecular and genetic bases of rare diseases affecting the hematopoietic system.
- Biology of hematopoietic transplantation.

Most relevant scientific articles

- S Navarro, V Moleiro, F.J. Molina-Estevez, M.L. Lozano, R Chinchon, E Almarza, O Quintana-Bustamante, G Mostoslavsky, T Maetzig, M Galla, N Heinz, B Schiedlmeier, Y Torres, U Modlich, E Samper, P Río, J.C. Segovia, A Raya, G Güenechea, J.C. Izpisua-Belmonte and J.A. Bueren. Generation of iPSCs from genetically corrected Brca2 hypomorphic cells: Implications in cell reprogramming and stem cell therapy. Stem Cells. Accepted manuscript online: 29 OCT 2013. DOI: 10.1002/stem.1586.
- Oviedo A, Yañez R, Colmenero I, Aldea M, Rubio A, Bueren JA, Lamana ML. Reduced efficacy of mesenchymal stromal cells in preventing graft-versus-host disease in an in vivo model of haploidentical bone marrow transplant with leukemia. Cell Transplant. 2013;22(8):1381-94. doi: 10.3727/096368912X657666. Epub 2012 Oct 4.
- Molina-Estevez FJ, Lozano ML, Navarro S, Torres Y, Grabundzija I, Ivics Z, Samper E, Bueren JA, Guenechea G. Impaired cell reprogramming in non homologous end joining deficient cells. Stem Cells. 2013 Aug;31(8):1726-30. doi: 10.1002/stem.1406.
- Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, Trujillo JP, Minguillón J, Ramírez MJ, Pujol R, Casado JA, Baños R, Rio P, Knies K, Zúñiga S, Benítez J, Bueren JA, Jaspers NG, Schärer OD, de Winter JP, Schindler D, Surrallés J. Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. Am J Hum Genet. 2013 May 2;92(5):800-6. doi: 10.1016/j.ajhg.2013.04.002. Epub 2013 Apr 25.
- Tremblay JP, Xiao X, Aartsma-Rus A, Barbas C, Blau HM, Bogdanove AJ, Boycott K, Braun S, Breakefield XO, Bueren JA, Buschmann M, Byrne BJ, Calos M, Cathomen T, Chamberlain J, Chuah M, Cornetta K, Davies KE, Dickson JG, Duchateau P, Flotte TR, Gaudet D, Gersbach CA, Gilbert R, Glorioso J, Herzog RW, High KA, Huang W, Huard J, Joung JK, Liu D, Liu D, Lochmüller H, Lustig L, Martens J, Massie B, Mavilio F, Mendell JR, Nathwani A, Ponder K, Porteus M, Puymirat J, Samulski J, Takeda S, Thrasher A, VandenDriessche T, Wei Y, Wilson JM, Wilton SD, Wolfe JH, Gao G. Translating the genomics revolution: the need for an international gene therapy consortium for monogenic diseases. Mol Ther. 2013 Feb;21(2):266-8. doi: 10.1038/mt.2013.4.

Highlights

This research line is focused on the development of novel therapies for rare diseases affecting the lympho-hematopoietic system. During 2013 we have progressed our studies anemia Fanconi anemia, erythrocyte pyruvate kinase deficiency, and primary immunodeficiency LAD- 1.

Among the most significant results obtained during 2013 we have verified the efficacy and safety of gene therapy protocols with a lentiviral vector designed in our laboratory for the treatment of Fanconi anemia. Also we have analysed the involvement of the NHEJ repair pathway in the reprogramming of adult cells to generate induced pluripotent stem cells (iPSCs). These studies have facilitated the development of a clinical trial for the gene therapy of Fanconi anemia, and have provided a new tool for understanding the role of NHEJ in cell reprogramming. Also related with the Fanconi anemia studies, we have generated for the first time gene corrected iPSCs from mice deficient in the BRCA2/FANCD1 gene, and have collaborated with the team of J. Surralles in the discovery of a new Fanconi anemia gene , and developed new transposons for the treatment of this disease.

Regarding the studies on the erythrocyte pyruvate kinase deficiency anemia, we have demonstrated the effectiveness of gene editing tools (TALE nuclease) for the generation of iPSCs from these patients. This allowed us to perform gene correction by homologous recombination in erythrocyte pyruvate kinase deficient cells. Finally, we have completed the development of a lentiviral vector for the treatment of pyruvate kinase deficiency by gene therapy, and will ask a designation of an Orphan Drug designation in the near future.

In the field of LAD-I immunodeficiency, the relevance of CD18 in hematopoietic stem cell function has been investigated using a mouse model of the disease. Additionally, a family of lentiviral vectors have been generated, whose functionality is under evaluation.

PROGRAMME:
Genetic Medicine

Group U711

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Main lines of research

- Genetics of neurological and neuromuscular diseases.
- Genetics of hereditary colorectal cancer.
- Genetics of hereditary breast and ovarian cancer.
- Pharmacogenetics: Adverse drug reactions.
- Genetics of ocular diseases.
- Genetics of cardiovascular diseases.
- Genetics of serious microorganism-host interactions.
- Characterization of new genes, mutations and genotype-phenotype relation in ataxias and hereditary spastic paraplegias.
- Bioinformatic tools for genetic databases.
- Integration of genetic and environmental data in models of RD etiology by means of geographic information systems (ecogeographic genetic epidemiology). Analysis of spatial patterns of rare diseases.
- Neurocognitive aspects in rare genetic diseases genetic: Williams syndrome and Smith-Magenis syndrome.

Most relevant scientific articles

- Transcriptome and genome sequencing uncovers functional variation in humans. Lappalainen T, Sammeth M, Friedländer MR, 't Hoen PA, Monlong J, Rivas MA, Gonzàlez-Porta M, Kurbatova N, Griebel T, Ferreira PG, Barann M, Wieland T, Greger L, van Iterson M, Almlöf J, Ribeca P, Pulyakhina I, Esser D, Giger T, Tikhonov A, Sultan M, Bertier G, MacArthur DG, Lek M, Lizano E, Buermans HP, Padioleau I, Schwarzmayr T, Karlberg O, Ongen H, Kilpinen H, Beltran S, Gut M, Kahlem K, Amstislavskiy V, Stegle O, Pirinen M, Montgomery SB, Donnelly P, McCarthy MI, Flicek P, Strom TM; Geuvadis Consortium, Lehrach H, Schreiber S, Sudbrak R, Carracedo A, Antonarakis SE, Häsler R, Syvänen AC, van Ommen GJ, Brazma A, Meitinger T, Rosenstiel P, Guigó R, Gut IG, Estivill X, Dermitzakis ET, Palotie A, Deleuze JF, Gyllensten U, Brunner H, Veltman J, Cambon-Thomsen A, Mangion J, Bentley D, Hamosh A. Nature. 2013 Sep 26;501(7468):506-11. doi: 10.1038/nature12531. PMID: 24037378.
- Association of thromboxane A1 synthase (TBXAS1) gene polymorphism with acute urticaria induced by nonsteroidal anti-inflammatory drugs. Vidal C, Porras-Hurtado L, Cruz R, Quiralte J, Cardona V, Colás C, Castillo LF, Marcos C, Soto T, López-Abad R, Hernández D, Teresa Audicana M, Armisén M, Rodríguez V, Perez-Carral C, Moreno E, Cabañes R, Corominas M, Parra A, Lobera T, Quiñones D, Ojeda P, Luna I, Torres M, Carracedo A. J Allergy Clin Immunol 2013 Jun 10. pii: S0091-6749(13)00692-1. doi: 10.1016/j.jaci.2013.04.045. [Epub ahead of print] FI: 12,047.
- Somatic MLH1 promoter hypermethylation is a frequent event in lynch syndrome colorectal cancers. Moreira, L.; Munoz, J.; Cuatrecasas, M.; Quintanilla, I.; Leoz, ML.; Carballal, S.; Ocana, T.; Fernández, P.; Arnold, M.; Pellise, M.; Jover, R.; Andreu, M.; Carracedo, A.; Llor, X.; Boland, CR.; Goel, A.; Castells, A. y Balaguer, F. Gastroenterology 2013 May. Volume: 144 Issue: 5 Supplement: 1 Pages: S25-S25 FI: 12,821.
- Supercomplex assembly determines electron flux in the mitochondrial electron transport chain. Lapuente-Brun E, Moreno-Loshuertos R, Acín-Pérez R, Latorre-Pellicer A, Colás C, Balsa E, Perales-Clemente E, Quirós PM, Calvo E, Rodríguez-Hernández MA, Navas P, Cruz R, Carracedo A, López-Otín C, Pérez-Martos A, Fernández-Silva P, Fernández-Vizarra E, Enríquez JA. Science 2013 Jun 28;340(6140):1567-70. doi: 10.1126/science.1230381. FI: 31,027.
- Mutations in the gene encoding PDGF-B cause brain calcifications in humans and mice. Keller A, Westenberger A, Sobrido MJ, García-Murias M, Domingo A, Sears RL, Lemos RR, Ordoñez-Ugalde A, Nicolas G, da Cunha JE, Rushing EJ, Hugelshofer M, Wurnig MC, Kaech A, Reimann R, Lohmann K, Dobričić V, Carracedo A, Petrović I, Miyasaki JM, Abakumova I, Mäe MA, Raschperger E, Zatz M, Zschiedrich K, Klepper J, Spiteri E, Prieto JM, Navas I, Preuss M, Dering C, Janković M, Paucar M, Svenningsson P, Saliminejad K, Khorshid HR, Novaković I, Aguzzi A, Boss A, Le Ber I, Defer G, Hannequin D, Kostić VS, Campion D, Geschwind DH, Coppola G, Betsholtz C, Klein C, Oliveira JR. Nat Genet 2013 Aug 4. doi: 10.1038/ng.2723. [Epub ahead of print] FI: 35,209.

Highlights

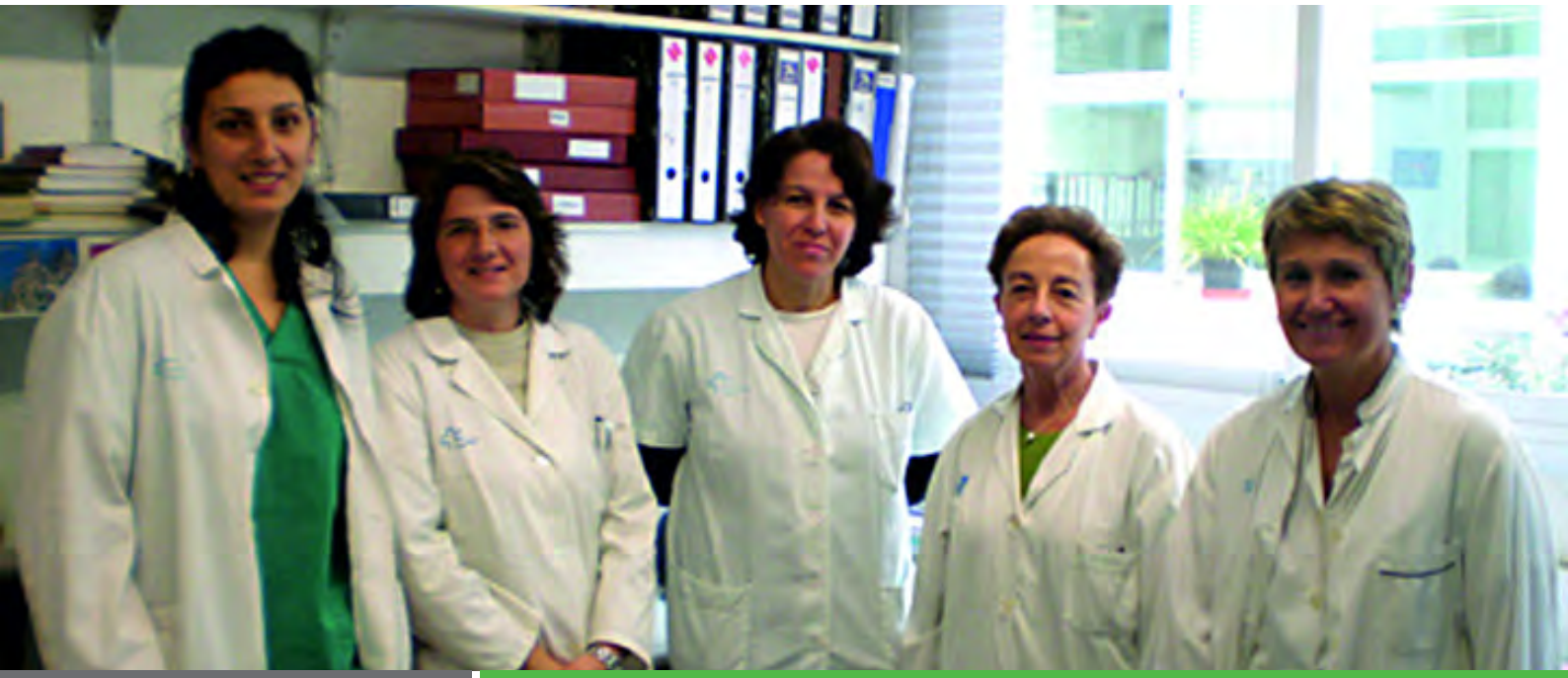
From the scientific point of view the most relevant were publications on high-impact journals of relevant research such as the identification of mutations in the gene encoding PDGF-B as cause of brain calcifications published in Nature Genetics and co-leaded by researchers of the group, together with basic research on mitochondrial DNA function (Lapuente et al. Science)and on RNA seq that can have a profound impact in the research of rare diseases.

Regarding projects the participation in a number of European projects is remarkable including CHIBCHA,GEUVADIS, REQUITE, HELIX and EU-GEI and a number of European or international Consortium. It is also important the collaboration the private-public collaboration with projects such as LC-NGS APLICLINIC for the generation of bioinformatics tools for next generation sequencing translation to clinical practice.

We have also collaborated in a number of clinical guidelines and actions at local, national, international level such us the elaboration of genetic diagnosis schemes for inherited cancer and intellectual disability and autism in Galicia, Fragile-X syndrome at national level and an intensive work in the interdisciplinary committee at the IRDiRC.

Two spin-off of the group were launched in 2013 one dealing with genetic counseling and a second with pharmacogenetics.

Finally we have launched the project Innopharma for early drug discovery were a number a high throughput screening for molecules for targets of different diseases were approved and rare diseases prioritized (and two projects on rare diseases supported).



PROGRAMME:
Endocrine Medicine

Group U712

Group Members

STAFF MEMBERS

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Main lines of research

- Genetic regulation of growth in control an delayed growth populations: genes GH1, GHR, GHRHR, IGF-1, IGF1R, VDR.
- Hormone and growth factor regulation of proliferation and gene expression in growing human cartilage.
- Analysis of new genes involved in human sex differentiation: AR, SRD5A2, HSD17B3, CYP17A1, CYP19A1, StAR, SF1, MAMLD1, GATA4. Search of new genes.
- Genes involved in congenital isolated glucocorticoid deficiency: genes MC2R, MRAP, StAR, CYP11A1.
- Epidemiological and genetic factors involved in raquitism. Genes VDR, MC1R, TYR1, TYRP1-1, TYRP1-2, OCA2-1, OCA2-2, SLC45A2-1, SLC45A2-2, SLC24A5-1, KITLG-1.

Most relevant scientific articles

- Labarta JI, Barrio E, Audí L, Fernández-Cancio M, Andaluz P, de Arriba A, Puga B, Calvo MT, Mayayo E, Carrascosa A, Ferrández-Longás A. Familial short stature and intrauterine growth retardation associated with a novel mutation in the IGF-I receptor (IGF1R) gene. Clin Endocrinol (Oxf). 2013 Feb;78(2):255-62. doi: 10.1111/j.1365-2265.2012.04481.x. PubMed PMID: 22738321.
- Audí L, Carrascosa A. Clinical usefulness of growth hormone secretion elicited by acute stimulation tests. Clin Endocrinol (Oxf). 2013 Aug;79(2):168-9. doi: 10.1111/cen.12173. Epub 2013 May 20. Erratum in: Clin Endocrinol (Oxf). 2013 Dec;79(6):904. Laura, Audí [corrected to Audí, Laura]; Antonio, Carrascosa [corrected to Carrascosa, Antonio]. PubMed PMID: 23442210.
- Carrascosa A, Audí L, Fernández-Cancio M, Yeste D, Gussinye M, Campos A, Albisu MA, Clemente M, Bel J, Nosás R, Rabanal M, Del Pozo C, Gómez JM, Mesa J; Group for Short Stature Study. Height gain at adult-height age in 184 short patients treated with growth hormone from prepubertal age to near adult-height age is not related to GH secretory status at GH therapy onset. Horm Res Paediatr. 2013;79:145-56. doi: 10.1159/000348540. Epub 2013 Mar 28. PubMed PMID: 23548791.
- Wit JM, Ranke MB, Albertsson-Wikland K, Carrascosa A, Rosenfeld RG, Van Buuren S, Kristrom B, Schoenau E, Audi L, Hokken-Koelega AC, Bang P, Jung H, Blum WF, Silverman LA, Cohen P, Cianfarani S, Deal C, Clayton PE, de Graaff L, Dahlgren J, Kleintjens J, Roelants M. Personalized approach to growth hormone treatment: clinical use of growth prediction models. Horm Res Paediatr. 2013;79(5):257-70. doi: 10.1159/000351025. Epub 2013 May 28. PubMed PMID: 23735882.
- Fernández-Rebollo E, Lecumberri B, Gaztambide S, Martínez-Indart L, Perez de Nanclares G, Castaño L; Spanish PHP Group. Endocrine profile and phenotype-(epi)genotype correlation in Spanish patients with pseudohypoparathyroidism. J Clin Endocrinol Metab. 2013 May;98(5):E996-1006. doi: 10.1210/jc.2012-4164. Epub 2013 Mar 26. PubMed PMID: 23533243.

Highlights

MAIN ACHIEVEMENTS

- Update the skeletal growth charts for premature and term infants and normal children to final height in the Spanish population. Obtain the different growth charts for the 5 sex-specific growth spurt onset groups in the normal population. Design and distribute a free-use programme for anthropometric evaluation (AuxoLog®: http://www.estudiosdecrecimiento.es). Collaboration with other paediatric endocrinology groups in Spain.
- Characterise the molecular basis of chronic harmonic growth retardation in a paediatric population (to date: GH1, GHRH, GHRHR, GHR, IGF1R). Collaboration with other national and international paediatric endocrinology groups.
- Analyse the relevance of clinical, biochemical and molecular diagnostic criteria to the classification of children with harmonic growth retardation and their reponse to GH therapy at the end of the 1st and 2nd years, at age of onset of the pubertal growth spurt and at final height. Collaboration with the Advisory Board of Catalan Government.
- Characterise the molecular basis for early-onset adrenal insufficiency in children through candidate gene sequencing (to date: MC2R, MRAP, StAR, CYP11A1). Collaboration with one international paediatric endocrinology group.
- Characterise the molecular basis for 46,XY DSD (to date: NR5A1, MAMLD1, LHCGR, StAR, CYP11A1, CYP17A1, HSD17B3, SRD5A2, AR). Collaboration with national and international paediatric endocrinology groups.

FUNDING

- Catalan Government funding: Consolidated Group of the Catalan Research Agency (2009SGR31).
- BMBS COST Action BM1303 - A systematic Elucidation of Differences of Sex Development (DSDnet). MoU 003/13. CSO Approval 16/05/2013. Start of Action 07/11/2013. End of Action 06/11/2017.
- Pharmaceutical industry funding:

  Ipsen: Increlex® (IGF-1) therapy database (NextOne Project) / Lilly: SHOX gene analysis / Pfizer: international collaborative pharmacogenetic study on responsiveness to GH therapy anthropometric growth studies obesity programme

PROGRAMME:
Mitochondrial Medicine

Group U713

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Main lines of research

- Alterations of biogenesis and/or mitochondrial functions in human pathology due to genetic or epigenetic causes.
- Biosynthesis, assembling and degradation of the mitochondrial oxidative phosphorylation Complex V. Identification and functional characterization of the mRNA binding proteins from the beta-F1-ATPasa subunit.
- Development of cellular and mouse models of disease with alterations in mitochondrial oxidative phosphorylation.
- Development of proteomic platforms for the identification of molecular markers of diagnosis in rare diseases related to energy metabolism.
- Protein expression and development of monoclonal antibodies against mitochondrial proteins and energy metabolism to be used in mitochondrial pathologies diagnostic kits.

* At the expense of Project

Most relevant scientific articles

- Formentini L, Pereira MP, Sánchez-Cenizo L, Santacatterina F, Lucas JJ, Navarro C, Martínez-Serrano A, Cuezva JM. (2014) In vivo inhibition of the mitochondrial H+-ATP synthase in neurons promotes metabolic preconditioning. EMBO J. 33(7):762-78.
- Sánchez-Aragó M., García-Bermúdez J., Martínez-Reyes I., Santacatterina F., Cuezva JM. (2013) Degradation of IF1 controls energy metabolism during osteogenic differentiation of stem cells. EMBO Rep. 14(7):638-44.
- Sánchez-Aragó M., Formentini L., Martínez-Reyes I., García-Bermudez J., Santacatterina F., Sánchez-Cenizo L., Willers IM., Aldea M., Nájera L., Juarránz A., López EC., Clofent J., Navarro C., Espinosa E., Cuezva JM. (2013) Expression, regulation and clinical relevance of the ATPase inhibitory factor 1 in human cancers. Oncogenesis. 2:e46.
- López-Erauskin J., Galino J., Ruiz M., Cuezva JM., Fabregat I., Cacabelos D., Boada J., Martínez J., Ferrer I., Pamplona R., Villarroya F., Portero-Otín M., Fourcade S., Pujol A. (2013) Impaired mitochondrial oxidative phosphorylation in the peroxisomal disease X-linked adrenoleukodystrophy. Hum Mol Genet. 22(16):3296-305.
- Sánchez-Aragó, M., Formentini, L., Cuezva, JM. (2013) Mitochondria-Mediated Energy Adaption in Cancer: The H(+)-ATP Synthase-Geared Switch of Metabolism in Human Tumors. Antioxid Redox Signal. 19(3):285-98.

Highlights

PROJECTS

Reference: BFU2010-18903. Title: Biogénesis de la mitocondria y su disfunción en patología. Budget: 363.000€. 2011-2013. PI: José M. Cuezva Marcos.

Reference: S2010/BMD-2402. Title: La mitocondria y su implicación en patología humana. Budget: 795.800€. 2012-2015. PI: José M. Cuezva Marcos.

PATENTES

Inventors: Fulvio Santacatterina, María Sánchez-Aragó and José M. Cuezva. Title: "Un proceso y kit para el diagnóstico diferencial de una enfermedad que cursa con afectación muscular". Application number: 201230771. Publication number: ES2432653. Country: Spain. Publication date: 23/05/2012. Applicants: Universidad Autónoma de Madrid-CIBERER.

BRAND REGISTRY NUMBER: PROTEOmAb.

Owner: Universidad Autónoma de Madrid. Brand number: 3.055.803. Application date: 12/12/2012. Authorization date: 14/03/2013.

The lab has developed PROTEOmAb Platform, focused on identification and quantification of new disease molecular markers and/or therapy response. Based on "Reverse Phase Protein Microarray" technology. Analysis of 1.000 different biopsies, that provides correlations with clinical and treatment response parameters.

(i) "Translation of Energy Metabolism" group in Cancer field of the Instituto de Investigación Hospital 12 de Octubre (i+12)

(ii) We belong to MITOLAB Consortium, Comunidad de Madrid. J.M. Cuezva is the Coordinator.

ABSTRACT OF SELECTED PUBLICATIONS

We have demonstrate that the ATPase Inhibitory Factor 1 (IF1) is expressed in hMSCs but is not expressed in the differentiated cells. In a transgenic mouse model the expression of IF1 in neurone inhibits oxidative phosphorylation and regulates the activity of aerobic glycolysis. This also has been demonstrated in hMSCs. Activation of IF1 degradation acts as the switch that regulates energy metabolism during differentiation. We conclude that IF1 is a stemness marker important for maintaining the quiescence state and recently IF1 has been described as a negative regulator of mitochondrial respiratory defects in rare diseases (Cell Reports 7, 1-8, 2014).

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U714

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Main lines of research

- Design and development of new therapeutic tools for rare skin diseases based on cell and gene therapy.
- Adult epidermal stem cell biology and its use in regenerative medicine.
- Cutaneous regeneration: study of the molecular mechanisms involved in wound repair and identification of new therapeutic targets.
- Study of the molecular basis of inherited ampollous diseases: Epidermolisis Bullosa and Kindler síndrome.
- Development of humanized animal models of rare skin diseases.
- Bone regeneration through tissue engineering.

Most relevant scientific articles

- Chamorro C, Almarza D, Duarte B, Llames SG, Murillas R, García M, Cigudosa JC, Espinosa-Hevia L, Escámez MJ, Mencía A, Meana A, García-Escudero R, Moro R, Conti CJ, Del Río M, Larcher F. Keratinocyte cell lines derived from severe generalized recessive epidermolysis bullosa patients carrying a highly recurrent COL7A1 homozygous mutation: models to assess cell and gene therapies in vitro and in vivo. Exp Dermatol. 2013; 22(9):601-3. doi: 10.1111/exd.12203.
- Sanchez-Jimeno C, Cuadrado-Corrales N, Aller E, García M, Escámez MJ, Illera N, Trujillo-Tiebas MJ, Ayuso C, Millán JM, Del Río M. Recessive dystrophic epidermolysis bullosa: the origin of the c.6527insC mutation in the Spanish population. Br J Dermatol. 2013;168(1):226-9. doi: 10.1111/j.1365-2133.2012.11128.x.
- Aufenvenne K, Larcher F, Hausser I, Duarte B, Oji V, Nikolenko H, Del Rio M, Dathe M, Traupe H. Topical enzyme-replacement therapy restores transglutaminase 1 activity and corrects architecture of transglutaminase-1-deficient skin grafts. Am J Hum Genet. 2013; 93(4):620-30. doi: 10.1016/j.ajhg.2013.08.003.
- Puig-Butille JA, Escámez MJ, García-García F, Tell-Marti G, Fabra A, Martínez-Santamaría L, Badenas C, Aguilera P, Pevida M, Dopazo J, Del Río M, Puig S. Capturing the biological impact of CDKN2A and MC1R genes as an early predisposing event in melanoma and non melanoma skin cancer. Oncotarget. 2013; 5 (6): 1439-51.
- Coluccio A, Miselli F, Lombardo A, Marconi A, Malagoli Tagliazucchi G, Gonçalves MA, Pincelli C, Maruggi G, Del Rio M, Naldini L, Larcher F, Mavilio F, Recchia A. Targeted gene addition in human epithelial stem cells by zinc-finger nuclease-mediated homologous recombination. Mol Ther. 2013; 21(9):1695-704.

Highlights

The Unit 714 conducts basic and translational research on rare dermatological diseases, such as Epidermolysis Bullosa, Netherton syndrome, congenital Pachyonychia, Xeroderma Pigmentosum and Kindler syndrome, among others. During 2013 a national clinical trial was awarded and we become partners of the GENEGRAFT European project, the first clinical trial of Gene Therapy for Epidermolysis Bullosa which is entirely based on a strategy published and patented by our group.

Additionally, our Unit collaborated with various Spanish hospitals in the treatment of chronic ulcers (bioengineered skin/cell therapy) in the context of COMPASSIONATE USE. Also noteworthy is the transfer of the know-how for the production of dermal substitutes to the Cell Therapy Unit of the Hospital Niño Jesus. Also at translational level must be highlighted the activities of our unit in the molecular diagnosis of the different forms of epidermolysis. This activity is recorded in ORPHANET and currently funded by CIEMAT. Finally, U714 has participated in creating patient REGISTRIES and carrying out epidemiological studies in collaboration with ISCIII-Rare Disease Institute, other CIBERER Units and clinical researchers from various hospitals.

Concerning transfer activity during 2013, it is remarkable the creation of a SPIN-OFF and the exploitation of two of our patents for the treatment of skin and bone rare diseases.

In 2013, U714 has been funded by Public National (1 project from SAF, 1 project from FIS, 1 project from the Ministry of Health and Social Policy: Clinical Trial and 1 INNPACTO project) and Regional grants (2 projects from CAM) as well as private grants (1 project from Ramón Areces Foundation). The group also received European funding (Eranet project outsourcing). Finally, is worthy to mention the granting of two intramural projects (ACCI).

PROGRAMME:
Genetic Medicine

Group U715

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Main lines of research

- Transcriptomics: Microarrays and ultra-sequencing data analysis.
- Genotyping (GWAS) from both microarrays and ultra-sequencing.
- Functional analysis of data from genomic experiments from the systems biology perspective. Use of non structured functional modules such as Gene Ontology (GO) and structured such as pathways, protein interaction networks or transcriptional networks.
- Development of software for the analysis and integration of genomic data. Babelomics project (http://www.babelomics.org).
- Systems biology approach to the study of rare diseases.
- Analysis and use of different ultra-sequencing data. In addition to transcriptomics (RNA-seq) and variation analysis, Chip-seq, copy number variation (CNV) and other chromosome alterations (translocations, inversions…) are studied.

Most relevant scientific articles

- Sebastián-León P, Carbonell J, Salavert F, Sanchez R, Medina I, Dopazo J. 2013. Inferring the functional effect of gene expression changes in signaling pathways. Nucleic Acids Res. 41:W213-7.
- Fernández RM, Bleda M, Luzón-Toro B, García-Alonso L, Arnold S, Sribudiani Y, Besmond C, Lantieri F, Doan B, Ceccherini I, Lyonnet S, Hofstra RM, Chakravarti A, Antiñolo G, Dopazo* J, Borrego* S. 2013. Pathways systematically associated to Hirschsprung's disease. Orphanet J Rare Dis. 8(1):187.
- Medina I, Salavert F, Sanchez R, de Maria A, Alonso R, Escobar P, Bleda M, Dopazo J. 2013 Genome Maps, a new generation genome browser. Nucleic Acids Res. 41:W41-6.
- de Castro-Miró M, Pomares E, Lorés-Motta L, Tonda R, Dopazo J, Marfany G, Gonzàlez-Duarte R. 2014. Combined genetic and high-throughput strategies for molecular diagnosis of inherited retinal dystrophies. PLoS ONE.;9(2):e88410.
- Dopazo J. 2013 Genomics and transcriptomics in drug discovery. Drug Discov Today.19(2):.126-132.

Highlights

The main objective of the group is the analysis of genomic data, especially in the context of rare diseases, from a computational and Systems biology perspective. These aims confer a horizontal character to the group, with a clear translational objective.

The most relevant results of the group include several computational tools, among which the genomic viewer, Genomemaps (Medina et al., 2013, NAR) deserves to be cited. This tool enables the representation of different genomic features in the context of the genome using an intelligent technology based on Google Maps, which can cope with huge data transfers interactively. A proof of its efficiency is the fact that the International Cancer Genome Consortium (ICGC) has chosen Genome Maps as the official genome viewer of the consortium (see the ICGC data portal: http://dcc.icgc.org/), where is used by thousands of researchers around the world

Using all the developments for genomic data analysis we have participated in the analysis of numerous whole exome sequencing (WES) experiments of a large number of cases, some of which started to be published during 2013. For example, our analyses discovered new mutations with clear diagnostic potential in metabolic diseases (Tort et al., 2013, Mol Genet Metab), degenerative retinal dystrophies (Méndez-Vidal et al., 2013 Mol Vis) or gut neurocristopathies (Fernandez et al., 2013 Orphanet J Rare Dis.)

The most strategic aspect of our work is the interpretation of genomic data. Recently, we have focused on the study of the impact of gene deregulations or mutations in signaling pathways and the corresponding functional consequences. We have developed a web tool that allows transforming genomic data into phenotypic consequences, revealing in this way details on the molecular mechanisms of the disease that otherwise would remain undiscovered (Sebastián-León et al., NAR).

PROGRAMME:
Pediatric and Developmental Medicine

Group U716

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Main lines of research

- Gene therapy.
- Characterization of factors associated with familial pancreatic cancer.
- Mouse models for neuropsychiatric disorders.
- Neurodegeneration.
- Mental retardation.
- Molecular and cellular basis of chromosome 21 aneuploidies.

Most relevant scientific articles

- Triplication of DYRK1A causes retinal structural and functional alterations in Down syndrome. Laguna A, Barallobre MJ, Marchena MÁ, Mateus C, Ramírez E, Martínez-Cue C, Delabar JM, Castelo-Branco M, de la Villa P, Arbonés ML. Hum Mol Genet. 2013 Jul 15;22(14):2775-84. PMID: 23512985.
- Environmental enrichment rescues DYRK1A activity and hippocampal adult neurogenesis in TgDyrk1A. Pons-Espinal M, Martínez de Lagran M, Dierssen M. Neurobiol Dis. 2013 Dec;60:18-31. PMID: 23969234.
- Normalization of Dyrk1A expression by AAV2/1-shDyrk1A attenuates hippocampal-dependent defects in the Ts65Dn mouse model of Down syndrome. Altafaj X, Martín ED, Ortiz-Abalia J, Valderrama A, Lao-Peregrín C, Dierssen M, Fillat C. Neurobiol Dis. 2013 Apr;52:117-27. PMID: 23220201.
- Hippocampal hyperexcitability underlies enhanced fear memories in TgNTRK3, a panic disorder mouse model. Santos M, D'Amico D, Spadoni O, Amador-Arjona A, Stork O, Dierssen M. J Neurosci. 2013 Sep 18;33(38):15259-71. PMID: 24048855.
- Intraductal delivery of adenoviruses targets pancreatic tumors in transgenic Ela-myc mice and orthotopic xenografts. José A, Sobrevals L, Miguel Camacho-Sánchez J, Huch M, Andreu N, Ayuso E, Navarro P, Alemany R, Fillat C. Oncotarget. 2013 Jan;4(1):94-105. PMID: 23328228.

Highlights

The team focuses its research on the study of the molecular basis, the pathophysiological mechanisms and therapeutic approaches of neurodevelopmental genetic diseases with a special interest on aneuploidies associated to human chromosome 21 (HSA21). Moreover, the group develops therapeutic strategies for rare tumours. In 2013, the group contributions have shown that overexpression of the HSA21 gene DYRK1A involves neurodevelopmental alterations that contribute to phenotypes associated with Down syndrome (DS), such are the motor phenotypes and the cellular and electrophysiological alterations of the retina. Our results have also shown that, in the adult, DYRK1A overexpression is linked to deleterious effects of the cholinergic system, as well as changes in synaptic plasticity and neurogenesis in hippocampus. Alterations in adult neurogenesis have been partially rescued by a pharmacological inhibitor of the kinase. The pathological contribution in a trisomic context has been evidenced by the attenuation of the synaptic plasticity defects achieved after normalization of Dyrk1A expression in trisomic mice by gene therapy. Regarding RCAN1, another key gene in DS, the group has helped to show that its overexpression is associated with the immune system dysfunction in DS .

We highlight two achievements of the group in 2013: 1) the development of a clinical trial (NCT01699711) in collaboration with the IMIM-Hospital del Mar on the "Use of epigallocatechin gallate in modulating Dyrk1A and APP and assess its impact on the cognitive performance in patients with Down syndrome " and 2) the granting of the XIII Ramon Trias Fargas Research Award 2013 on Down syndrome to the work " Understanding Down syndrome with the help of viruses " presented by our group.

PROGRAMME:
Mitochondrial Medicine

Group U717

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Main lines of research

- Identification and characterization of new proteins involved in the regulation of the OXPHOS system.
- Functional analysis by means of transmitochondrial cybrids of mutations identified in the mitochondrial genome associated with LHON and neurosensorial deafness.
- Molecular characterization of patients with intergenomic communication defects.
- Mitochondrial diseases with predominant phenotypic expression in cardiac muscle: Molecular characterization and analysis by means of transmitochondrial cybrids of new mutations identified in the mitochondrial genome.
- Development of animal models of mitochondrial diseases in Drosophila melanogaster.
- Generation of iPS cells harboring mutations in structural and regulator genes of the OXPHOS function.

Most relevant scientific articles

- Zambrano A, García-Carpizo V, Gallardo ME, Villamuera R, Gómez-Ferrería MA, Pascual A, Buisine N, Sachs LM, Garesse R, Aranda A. The thyroid hormone receptor BETA; induces DNA damage and premature senescence. J Cell Biol. (Figura del artículo seleccionada como portada de la revista). ISSN 0021-9525. 2014/ 204(1)/ 129-46. D.O.I. 10.1083/jcb.201305084.
- Fernández-Moreno MA, Hernández R, Adán C, Roberti M, Bruni F, Polosa PL, Cantatore P, Matsushima Y, Kaguni LS, Garesse R. Drosophila nuclear factor DREF regulates the expression of the mitochondrial DNA helicase and mitochondrial transcription factor B2 but not the mitochondrial translation factor B1. BBA-Gene Regul Mech. ISSN 1874-9399. 2013/ 1829(10)/ 1136-46. D.O.I. 10.1016/j.bbagrm.2013.07.006.
- Clemente P, Peralta S, Cruz-Bermudez A, Echevarría L, Fontanesi F, Barrientos A, Fernández-Moreno MA, Garesse R. hCOA3 stabilizes cytochrome c oxidase 1 (COX1) and promotes cytochrome c oxidase assembly in human mitochondria. J Biol Chem ISSN 0021-9258. 2013/ 288(12)/ 8321-8331. D.O.I. 10.1074/jbc.M112.422220.
- Gallardo ME, García-Pavía P, Chamorro R, Vázquez ME, Gómez-Bueno M, Millán I, Almoguera B, Domingo V, Segovia J, Vilches C, Alonso-Pulpón L, Garesse R, Bornstein B. Mitochondrial haplogroups associated with end-stage heart failure and coronary allograft vasculopathy in heart transplant patients. Eur Heart J. ISSN 0195-668X. 2012/ 33(3)/ 346-53 D.O.I. 10.1093/eurheartj/ehr280.
- Peralta S, Clemente P, Sánchez-Martínez A, Calleja M, Hernández-Sierra R, Matsushima Y, Adán C, Ugalde C, Fernández-Moreno MÁ, Kaguni LS, Garesse R. Coiled coil domain-containing protein 56 (CCDC56) is a novel mitochondrial protein essential for cytochrome c oxidase function. J Biol Chem. ISSN: 0021-9258. 2012/ 287(29)/ 24174-24185. D.O.I. 10.1074/jbc.M112.343764.

Highlights

The main aims of the CIBERER U717 unit have been focused on the study of different aspects of the mitochondrial physiopathology. The most relevant results during 2013 are:

- The identification of new genes probably involved in mitochondrial diseases (MD) (GatC and hCOA3). The results have been reported in 5 articles (2 in J Cell Science, 1 in JBC and 1 in BJ).
- The functional characterization of transmitochondrial cybrids obtained from patients with LHON and evaluation of the potential tumorigenicity of mitochondrial DNA mutations. With the results obtained we are now drafting two manuscripts.
- Analysis of the involvement of the thyroid hormone receptor beta in DNA damage and premature senescence. This work has been recently published in the outstanding journal (J. Cell Biol.).
- Molecular and functional characterization of mitochondrial and nuclear DNA mutations in patients with mitochondrial cardiomyopathy and analysis of the mitochondrial DNA background in the development of end stage heart failure. This work has been published in several journals. One in a first decile journal, Eur. Heart J., another in Mitochondrion and one in Circ. J. All of them have been signed as first or corresponding author by Dr. Gallardo (who is granted by CIBERER).
- Generation of induced pluripotent stem cells (iPSC) as a disease model and as a future approach for the treatment of MD. To perform this task we have been funded by an ACCI project during 2013 (13-717/132.05), another project that has finished in December 2013 (PI10/00703) and another one recently awarded (PI13/00556: January 14- December 2016). At this moment, we have generated several iPSC from patients with MD that are being characterized. This research line (supervised by Dr. Gallardo) and another one whose main aim is the identification of new OXPHOS genes will be the main research lines of our group in the next years.

PROGRAMME:
Sensorineural Pathology

Group U718

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Main lines of research

- Study of the genetic and molecular basis for retinal dystrophies.
- Direct mutational analysis of the genes responsible for hereditary retinal dystrophies.
- Construction and optimization of DNA chips for indirect diagnosis of the genes causing hereditary retinal dystrophies in isolated families. Application of the last version of the chip for the genetic diagnosis for 100 genes of retinal dystrophies.
- Search for new genes causing retinal dystrophies in affected families by means of exome/enrichment and massive DNA sequencing.
- Functional analysis of CERKL by means of studies in cell lines and of the animal model created by the team, knockout CERKL-/- mice.

Most relevant scientific articles

- Fathinajafabadi, A.; Pérez-Jiménez, E.;Riera, M.; Knecht, E; González-Duarte, R. CERKL, a retinal disease gene,encodes an mRNA-biding protein that localizes in compact and unstranslated mRNPs associated to microtubules. PLoS One 9 (2): e87898, 2014.
- Castro-Miró, M.; Pomares, E.; Lorés-Motta, L.; Tonda R.; Dopazo, J.; Marfany, G.; González-Duarte, R. Combined genetic and high-throughput strategies for the molecular diagnosis of inherited retinal dystrophies. PLoS One 9 (2): e88410, 2014.
- Riera, M.; Burguera, D.; García-Fernàndez, J.; Gonzàlez-Duarte, R. CERKL Knockdown Causes Retinal Degeneration in Zebrafish. PLoS One 8 (5) e64048, 2013.
- Garanto, A.; Mandal, N.A.; Egido-Gabás, M.; Marfany, G.; Fabriàs, G.; Anderson, R.E.; Casas, J.; Gonzàlez-Duarte, R. Specific sphingolipid content decrease in Cerkl knockdown mouse retinas. Experimental Eye Research 110: 96-106, 2013.
- Garanto A.; Vicente-Tejedor J.; Riera M.; de la Villa P.; González-Duarte R.; Blanco R.; Marfany G. The use of alternative promoters turns a targeted knockout of the Retinitis Pigmentosa gene Cerkl into a knockdown with mild affectation of the retinal ganglion cell layer. Biochimica et Biophysica Acta-Molecular Basis of Disease 1822: 1258 -1269, 2012.

Highlights

- The function of CERKL (CERamide Kinase Like), a causative gene of retinitis pigmentosa and cone-rod dystrophy, still awaits characterization. To approach its cellular role, we have investigated the subcellular localization and interaction partners of the full length CERKL isoform in different cell lines, including a photoreceptor-derived cell line. We have shown that CERKLa is a main component of compact and untranslated mRNPs and that it associates with other RNP complexes such as stress granules, P-bodies and polysomes. These results support an unexpected role of CERKL in controlling the stability, transport and/or translation of mRNAs. These functions had not been reported previously for any member of the retinal disorders gene family and highlight new cellular pathways and molecular targets to be considered when investigating the pathogenic mechanisms of these diseases. (Ref 1)
- We have undertaken the construction and optimization of a comprehensive cosegregation RD-chip based on SNP genotyping and haplotype analysis to diagnose a panel of Spanish families. The RD-chip allowed to genotype 768 selected SNPs (closely linked to 100 RD causative genes) in a single cost-, time-effective step. Full diagnosis was attained in 17/36 Spanish pedigrees, yielding 12 new and 12 previously reported mutations in 9 RD genes. The most frequently mutated genes were USH2A and CRB1. The chip analysis also highlighted families for novel RD gene search. Overall, the RD-chip diagnosis efficiency is over 47%, well within the upper range of the massive sequencing approaches used at present. (Ref 2)
- Cerkl is a single copy gene with a major isoform that is expressed in the retina of zebrafish (Danio rerio). Morpholino injection has been used to generate a Cerkl knockdown model of retinal degeneration in this animal. Cerkl expression has been decreased by 95%. The morphant phenotype results in abnormal eye development with lamination defects, failure to develop photoreceptor outer segments, increased apoptosis of retinal cells and small eyes. This zebrafish model is a powerful tool to unveil CERKL contribution to human retinal degeneration. (Ref 3)

PROGRAMME:
Pediatric and Developmental Medicine

Group U719

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Main lines of research

- Fetal and perinatal neurological damage.
- Diseases of placental origin and fetal programming of post-natal cardiac dysfunction.
- Highly complex fetal surgery: complications of monochorial twin pregnancy and congenital diaphragmatic hernia.
- Prenatal diagnosis of genetic and chromosomal abnormalities.
- Inherited metabolic diseases (IMD)
- Oxidative stress, antioxidant potential and premature cellular senescence in Down syndrome and Cockayne syndrome.
- Research on the pathogenic mechanisms of lysosomal disease.

Most relevant scientific articles

- Sanz-Cortes M, Carbajo RJ, Crispi F, Figueras F, Pineda-Lucena A, Gratacos E. Metabolomic profile of umbilical cord blood plasma from early and late intrauterine growth restricted (IUGR) neonates with and without signs of brain vasodilation. PLoS One 2013;8:e80121.
- Muñoz-Moreno E, Arbat-Plana A, Batalle D, Soria G, Illa M, Prats-Galino A, et al. A magnetic resonance image based atlas of the rabbit brain for automatic parcellation. PLoS One 2013;8:e67418.
- Illa M, Eixarch E, Batalle D, Arbat-Plana A, Muñoz-Moreno E, Figueras F, et al. Long-term functional outcomes and correlation with regional brain connectivity by MRI diffusion tractography metrics in a near-term rabbit model of intrauterine growth restriction. PLoS One 2013;8:e76453.
- Valenzuela-Alcaraz B, Crispi F, Bijnens B, Cruz-Lemini M, Creus M, Sitges M, et al. Assisted reproductive technologies are associated with cardiovascular remodeling in utero that persists postnatally. Circulation 2013;128:1442–50.
- Batalle D, Muñoz-Moreno E, Figueras F, Bargalló N, Eixarch E, Gratacos E. Normalization of similarity-based individual brain networks from gray matter MRI and its association with neurodevelopment in infants with intrauterine growth restriction. Neuroimage 2013;83:901–11.

Highlights

The unit 719 consists of a clinical and basic research team. It is one of the few groups in Spain specialized in fetal medicine. Among our main areas of research, we are focus on fetal diseases and pregnancy conditions classified as rare diseases, such as fetal malformations, preeclampsia or acute respiratory distress of the newborn. The research aims to (1) understand pathophysiological mechanisms and fetal programming, (2) develop biochemical and imaging biomarkers, (3) develop new therapies. The group is interdisciplinary and has clinicians, biologists and bioengineers.

Some of our major scientific and translational milestones achieved in 2013 include:

- Characterization of the effects of fetal growth restriction and congenital heart diseases using imaging biomarkers (Neuroimage 2013, PLoS One 2013).
- In fetal cardiology, development of methods for the study of fetal cardiac function, and characterization of the impact of different diseases on the fetal cardiac function. For the first time, we have shown that assisted reproduction is associated with cardiovascular programming in children (Circulation 2013)
- Consolidation of the first monographic fetal neurology unit, applying new biomarkers and screening protocols in fetal CNS.
- Establishment of the first fetal cardiac function unit in Spain, with distinct algorithms for predicting prognosis in congenital heart disease.
- Development of a new method of quantitative image analysis, in collaboration with our spin-off Transmural Biotech, for predicting the risk of neonatal respiratory distress. The patent application has been filed in late September 2013.
- Coordination of the FetalMed-PhD Project: the First Joint Doctorate in Fetal Medicine funded by the European Community - Erasmus Mundus Joint Doctorate. Total funding of € 5.92 million. Start Date: 2013.

PROGRAMME:
Inherited Metabolic Medicine

Group U720

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Main lines of research

- Study of the genetic and molecular basis of lysosomal diseases.
- Study of the genetic and molecular basis of the Costello syndrome.
- Homocysteine and pathology.
- Genetic basis of bone pathologies.
- Genetic basis of neurologic diseases.
- Genetic study of hereditary multiple hereditary multiple exostoses.
- Identification of the gene responsible for Opitz C syndrome by whole exome sequencing.

Most relevant scientific articles

- Sarrión P, Sangorrin A, Urreizti R, Delgado A, Artuch R, Martorell L, Armstrong J, Anton J, Torner F, Vilaseca MA, Nevado J, Lapunzina P, Asteggiano CG, Balcells S, Grinberg D. Mutations in the EXT1 and EXT2 genes in Spanish patients with multiple osteochondromas. Sci Rep. 3:1346, 2013.
- Yoskovitz G, García-Giralt N, Rodríguez-Sanz M, Urreizti R, Guerri R, Ariño-Ballester S, Prieto-Alhambra D, Mellibovsky L, Grinberg D, Nogues X, Balcells S, Diez-Perez A. Analyses of RANK and RANKL in the post-GWAS context: functional evidence of vitamin D stimulation through a RANKL distal region. J Bone Miner Res.28: 2550-60, 2013.
- Brands MM, Hoogeveen-Westerveld M, Kroos MA, Nobel W, Ruijter GJ, Ozkan L, Plug I, Grinberg D, Vilageliu L, Halley DJ, Ploeg AT, Reuser AJ. Mucopolysaccharidosis type VI phenotypes-genotypes and antibody response to galsulfase. Orphanet J Rare Dis. 8:51, 2013.
- Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, Neale BM, Faraone SV, ..., Cormand B, ..., et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013 Sep;45(9):984-94, 2013.
- Carreño O, Corominas R, Serra SA, Sintas C, Fernández-Castillo N, Vila-Pueyo M, Toma C, Gené GG, Pons R, Llaneza M, Sobrido MJ, Grinberg D, Valverde MÁ, Fernández-Fernández JM, Macaya A, Cormand B. Screening of CACNA1A and ATP1A2 genes in hemiplegic migraine: clinical, genetic, and functional studies. Mol Genet Genomic Med. 1:206-22, 2013.

Highlights

Our group investigates on the molecular genetic bases of monogenic as well as complex diseases. We also develop models for them and assay new therapeutic approaches. Some of the achievements of this year are:

Lysosomal diseases: A neuronal model for Sanfilippo C was obtained from iPS cells, which recapitulates the disease phenotype. We are also working on a mouse bearing a pseudoexon-generating mutation responsible for Niemann-Pick C disease, in which we will try an antisense oligonucleotide-based therapy.

Opitz C syndrome: as part of an exome project to identify novel genes for the disease, a new ASXL1 mutation was identified in one Bohring-Opitz patient.

Bone diseases: the mutational spectrum of a large group of Spanish and Latinamerican multiple osteochondromatosis patients was defined. Regarding the High Bone Mass phenotype, results of a genetic study demonstrated that this phenotype may have a monogenic or a multifactorial etiology in different patients. We are also undertaking the resequencing of loci associated with osteoprosis, to identify rare variants that may be true cause of the association.

Neuropsychiatric diseases: Rare autism-susceptibility variants have been discovered through the massive sequencing of exomes from multiplex autism families.

On the field of therapeutic applications, we have assayed various molecules potentially able to correct nonsense mutations, and products with chaperone activity, both for Gaucher disease and for GM1 gangliosidosis. This last project is undertaken through a collaboration with the Minoryx Therapeutics entreprise.

Funding was obtained at national level (SAF2011-25431, SAF2012-33484) as well as international (PIB2010AR-00473; FP7-HEALTH, EU, 602805-2).

PROGRAMME:
Genetic Medicine

Group U721

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Main lines of research

- Neuronal ceroid lipofuscinoses
- Danon disease
- Lafora disease
- X-linked adrenoleukodystrophy
- retinitis pigmentosa
- MELAS syndrome
- hereditary breast cáncer

Most relevant scientific articles

- Launay N, Ruiz M, Fourcade S, Schlüter A, Guilera C, Ferrer I, Knecht E, Pujol A (2013). Oxidative stress regulates the ubiquitin-proteasome system and immunoproteasome functioning in a mouse model of X-adrenoleukodystrophy. Brain 136, 891-904.
- Vidal-Donet JM, Cárcel-Trullols J, Casanova B, Aguado C, Knecht E (2013). Alterations in ROS activity and lysosomal pH account for distinct patterns of macroautophagy in LINCL and JNCL fibroblasts. PLoS One 8(2):e55526.
- Moruno-Manchón JF, Pérez-Jiménez E, Knecht E (2013). Glucose induces autophagy under starvation conditions by a p38 MAPK-dependent pathway. Biochem. J. 449, 497-506.
- García-Giménez JL, Seco-Cervera M, Aguado C, Romá-Mateo C, Dasí F, Priego S, Markovic J, Knecht E, Sanz P, Pallardó FV (2013). Lafora disease fibroblasts exemplify the molecular interdependence between thioredoxin 1 and the proteasome in mammalian cells. Free Radic. Biol. Med. 65, 347-359.
- Errafiy R, Aguado C, Ghislat G, Esteve JM, Gil A, Loutfi M, Knecht E (2013). PTEN increases autophagy and inhibits the ubiquitin-proteasome pathway in glioma cells Independently of its lipid phosphatase activity. PLoS One 8(12):e83318.

Highlights

Our laboratory, in addition to CIBER, is funded by the following agencies: "Marató" from TV3 (Ref. 110131), MINECO (Ref. BFU2011-22630) and the "Prometeo" program for excellence groups of the Valencian Community (Ref. 2012/ 061). We investigate the implications of alterations in intracellular protein degradation pathways and their regulation in rare diseases, including:

- Neuronal ceroid lipofuscinosis (NCL): Besides similarities, we have found differences between fibroblasts from patients with late infantile (LINCL/CLN2) and juvenile (JNCL/CLN3) NCL, which may explain the earlier onset of symptoms in the first. In CLN2 there is a greater accumulation of ROS produced by a loss in the activity of the TPP1 enzyme, whereas in CLN3 this loss is only partial and due to an increased lysosomal pH.
- Lafora disease: In collaboration with six other CIBER laboratories we are integrated in the Lafora Consortium that coordinately investigates this pathology. The most relevant aspects we have found in 2013 in all models of this disease are: i) a defective formation of autophagosomes, and ii) an increase in oxidative stress caused by defects in autophagy and in the antioxidant defence system, mainly in the mitochondrial isoform of superoxide dismutase and in catalase.
- X-Adrenoleukodystrophy: In collaboration with the 759U, we have found that autophagic flux is impaired and that this depends on mTOR activation.
- Retinitis pigmentosa (RP): In collaboration with the 718U we have shown that CERKL (Ceramide Kinase-Like), one of the proteins mutated in RP, is a component of compact and untranslated mRNPs, as well as of other RNPs complexes (stress granules, "P- bodies" and polysomes). CERKL interacts with different proteins such as eIF3B, PABP, HSP70 and RPS3, and binds to mRNAs through its amino-terminal part.

In addition, three PhD theses have been defended this year and have been awarded with "summa cum laude" (Ghita Ghislat, Félix Moruno and Rajaa Errafiy).

PROGRAMME:
Mitochondrial Medicine

Group U722

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Main lines of research

- Creation of the Group for Medical Assistance of Adult Patients with Rare Diseases (basically of metabolic and mitochondrial origen, among others).
- Mitochondrial Pathology: Mitochondrial basis of disease and cell processes.
- Muscular Pathology (mitochondrial, inflammatory, autoinmune and toxic).
- Toxicity induced by drugs that cause clinic manifestations of mitochondrial origen (Lipodystrophy, hyperlactatemia, peripheral neuropathy, infertility, obstetric problems, miopathy.)
- Toxicity induced by tobacco and carbon monoxide that cause clinic manifestations of mitochondrial origen.
- Mitochondrial basis of Parkinson disease associated to mutations in Parkin and LRRK2 genes (rare forms of the disease).
- Mitochondrial basis of body inclusion myositis.
- Mitochondrial function in the study of gene therapy in MNGIE.
- Mitochondrial implication in X-Fragile Syndrome.
- Mitochondrial basis on intrauterine growth restriction.

* At the expense of Project

Most relevant scientific articles

- Chewing-induced segmental myoclonus in a patient with Leigh syndrome. Navarro-Otano J, Valls-Solé J, Guaita M, Santamaria J, Cardellach F, Muñoz E. Mov Disord. 2013 Oct;28(12):1756-7. PMID: 23780927.
- Study of oxidative, enzymatic mitochondrial respiratory chain function and apoptosis in perinatally HIV-infected pediatric patients. Morén C, Garrabou G, Noguera-Julian A, Rovira N, Catalán M, Hernández S, Tobías E, Cardellach F, Fortuny C, Miró Ò. Drug Chem Toxicol. 2013 Oct;36(4):496-500. PMID: 23534415.
- First description of phosphofructokinase deficiency in spain: identification of a novel homozygous missense mutation in the PFKM gene. Vives-Corrons JL, Koralkova P, Grau JM, Mañú Pereira Mdel M, Van Wijk R. Front Physiol. 2013 Dec 30;4:393. PMID: 24427140.
- AGC1-malate aspartate shuttle activity is critical for dopamine handling in the nigrostriatal pathway. Llorente-Folch I, Sahún I, Contreras L, Casarejos MJ, Grau JM, Saheki T, Mena MA, Satrústegui J, Dierssen M, Pardo B. J Neurochem. 2013 Feb;124(3):347-62. PMID: 23216354.
- Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, Lozano E, Segarra M, García-Martínez A, Prieto-González S, Hernández-Rodríguez J, Grau JM, Rahman MU, Cid MC. Ann Rheum Dis. 2013 Sep 1;72(9):1481-7. PMID: 22993227.

Highlights

Our group is a multidisciplinary team of basic and clinic researchers with translational activity in the management of patients and research in the molecular basis, biomarkers and potential treatments for associated diseases. Along 2013 we have participated in:

- PIBER-1 with the PdI-Mitochondrial Medicine to study the EXOMA of patients with mitochondrial RD.
- PIBER-2 with units U701-U717-U723-U727 to study mitochondrial DNA maintenance syndromes, depletion and multiple deletions.
- PIBER-3 and 4 for clinic and therapeutic research in: (a) muscle pathology (gene therapy in MNGIE with units U701-U714 and research in new biomarkers in IBM with unit U703 or in poly/dermatomyosits with unit U713); (b) secondary mitochondriopathies (with units U701-U727); (c) mitochondrial implication in rare/common obstetric diseases (including IUGR with unit U719) or neurodegenerative disorders (including X-fragile syndrome with unit U726 or Parkinson disease with the CIBERNED). These projects, granted by 4 FIS,1 ACCI and 2 FIPSE, coexist with non granted projects with units U743-U713-U701-U727-U737.
- PITER-1 in: (a) diagnosis of RD (with units U701-U729-U717-U737); (b) translation to the NHS of diagnostic procedures (with units U717-U737-U701-U723-U727-U729); (c) clinical guidelines; and (d) the creation of the 'Unit of adult patients with inborn errors of metabolism' and the 'Work team in adult RD' integrated by units U703-U737-U722 and different services of the HCB.
- PITER-2 through the donation to the CIBERER-biobank of multiple samples from patients with RD.
- PITER-3 for the formation of students (in 2013 2 grade students; 3 master students; 2 PhD-students; 1 predoctoral CIBERER researcher; 5 residents), CIBERER tutorial program and university classes (grade/master).

We take part of mobility programs, CIBERER courses/meetings, publications, international congresses, clinical guidelines and consultant assistance of patients with RD directed to the CIBERER.

Our future perspective is directed to the translational research/diagnosis in RD, strengthen the 2 Units of patients with RD above mentioned.

PROGRAMME:
Mitochondrial Medicine

Group U723

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Main lines of research

- Mitochondrial diseases and exercise intolerance: Development and standardization of biochemical and genetic/genomic methods to improve the biochemical and genetic diagnosis. Identification of new disease-causing genes and novel mutations.
- Biochemical and molecular basis of mitochondrial respiratory chain complex I and complex III deficiencies.
- Assessment of OXPHOS complexes assembly by BN_PAGE and its clinical translation
- Neuromuscular diseases research lines: Metabolic Exercise Intolerance: i) Patient's registries, natural history and genotype-phenotype correlations of type V glycogenosis (GSDV- McArdle disease), ii) Amyotrophic Lateral Sclerosis: identifications of novel mutations, evaluation of pathophysiology of ALS using cell and animal models, and patient's clinical trials.
- Mitochondrial dynamics and autophagy: i) Role of mitochondrial dynamics and autophagy (and mitophagy) in cell models of mitochondrial disorders; ii) mitochondrial disturbances and autophagy pathway evaluation in a mouse model of graft vs host disease.
- Oxygen consumption as in vivo marker of mitochondrial disorders.
- Identification and validation of biomarkers in mitochondrial disorders.

Most relevant scientific articles

- Lucia A, Quinlivan R, Wakelin A, Martín MA, Andreu AL. The 'McArdle paradox': exercise is a good advice for the exercise intolerance. Br J Sports Med; 2013; 47:728-9.
- Delmiro A, Rivera H, García-Silva MT, Quijada-Fraile P, García-Consuegra I, Martín-Hernández E, Simón R, Moreno-Izquierdo A, Martín MA, Arenas J, Martínez-Azorín. Whole-Exome Sequencing Identifies a Mutation of the Mitochondrial MT-ND1 Gene Associated with epileptic encephalopathy: West síndrome evolving to Lennox-Gastaut síndrome. Hum Mutat 2013; 34:1623-7.
- Villar P, Bretón B, García-Pavía P, González-Páramos C, Blázquez A, Gómez-Bueno M, García-Silva T, García-Consuegra I, Martín MA, Garesse R, Bornstein B, Gallardo ME. Cardiac Dysfunction in Mitochondrial Disease. Circ J 2013; 77:2799-806.
- Barrientos A, Ugalde C. I Function, Therefore I Am: Overcoming Skepticism about Mitochondrial Supercomplexes. Cell Metab 2013; 18:147-9.
- García-Redondo A, Dols-Icardo O, Rojas-García R, Esteban-Pérez J, Cordero-Vázquez P, Muñoz-Blanco JL, Catalina I, González-Muñoz M,Varona L, Sarasola da P, Larrodé P, Capablo JL, Pascual-Calvet J, Goñi M, Morgado Y, Guitart M, Moreno-Laguna S, Rueda A, Martín-Estefanía C, Cemillán C, Blesa R, Lleó A. Analysis of the C9orf72 gene in patients with amyotrophic lateral sclerosis in Spain and different populations worldwide. Hum Mutat 2013; 34:79-82.

Highlights

In 2013 PIs of the group led 5 active projects of National Plan-ISCIII related to the lines of research: mitochondrial disorders, metabolic exercise intolerance and amyotrophic lateral sclerosis (ALS):

- Biomarkers and pathogenesis of ALS: Gene expression in lymphocytes and behavior of olfactory neuroepithelium stem cells;
- Development of a new strategy for the genetic diagnosis of mitochondrial diseases that are caused by nuclear genes;
- Identification and validation of biomarkers of mitochondrial diseases;
- Rate of oxygen consumption in mitochondrial diseases: from cell culture to clinical practice;
- Mitochondrial Medicine: a strategy for molecular genetics identification of OXPHOS patients (group coordinator; coordinated CIBERER U701).

We lead the WP Methodology and Registry EAHC the EU-project: European registry of patients with McArdle disease and very rare muscle glycogenolytic disorders (MGD) (PR-MDMGD). We headed non-public funded projects related mitochondrial disease and ALS (Biocross, Fundacion Mutua Madrileña, FUNDELA); and are also involved in Biosciences-Com. Madrid consortia where other CIBERER groups are involved U743; U717; U713. We participate in a clinical trial for ALS: Memantine (Ebixa) functional disability in amyotrophic lateral sclerosis. We lead an intramural project CIBERER (ACCI) in collaboration with U701 and U727) to identify genetic modifiers of homoplasmic mutations. The group as a clinical laboratory has achieved to move into the testing portfolio of our hospital the method to determine the mtDNA depletion that was previously approved in CIBERER as part of objectives of the Research Program Mitochondrial Medicine. The group is focusing on the use of new genetic methods and on the searching for biomarkers to improve diagnosis of mitochondrial diseases, and also is trying to understand its pathophysiology and to identify therapeutic targets using cellular and animal models; and it is also centered in the understanding the pathophysiology and the exercise as therapy in McArdle disease.

PROGRAMME:
Pediatric and Developmental Medicine

Group U724




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Main lines of research

- Research on cytogenetics and molecular genetics of infants born with malformations and other congenital defects.
- Research for the identification of teratogenic risk factors in humans and environmental causes of congenital defects in newborn infants.
- Research on the clinical and etiological aspects of infants born with malformations and other congenital defects.
- Research on the descriptive and analytical epidemiological aspects of infants born with malformations and other congenital defects.

Most relevant scientific articles

- Martínez-Frías ML, Martínez-Fernández ML. A highly specific coding system for the different structural chromosomal alterations. Am J Med Genet A. 2013 Apr, 161A:732–736. PMID: 23495121. doi: 10.1002/ajmg.a.35787. Epub 2013 Mar 12.
- Carrascosa-Romero MC, Suela J, Pardal Fernández JM , Bermejo-Sánchez E, Vidal Company A, MacDonald A, Tébar Gil R, Martínez-Fernández ML, Martínez-Frías ML. A 2.84 Mb deletion at 21q22.11 in a patient clinically diagnosed with Marden-Walker syndrome. Am J Med Genet A. 2013 Sep; 161(9): 2281-2290. PMID: 23894067. doi: 10.1002/ajmg.a.35862. Epub 2013 Jul 25.
- Vallejo OG, Benítez Sánchez M del C, Cánovas CS, Ontiveros JD, Ruiz Jiménez JI, Bermejo-Sánchez E, Martínez-Frías ML. Patient with disorganization syndrome: surgical procedures, pathology, and potential causes. Birth Defects Res A Clin Mol Teratol. 2013 Dec;97(12):781-785. PMID: 24307594. doi: 10.1002/bdra.23203. Epub 2013 Dec 4.
- Report: "Primary Prevention of Congenital Anomalies: Recommendations on Policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases". Autores: Domenica Taruscio and EUROCAT Primary Prevention Working Group, 2013. http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Reccomendations.pdf
- Sanchis Calvo A, Roselló-Sastre E, Marcos Puig B, Balanzá Chancosa R, Pérez Ebri ML, Alcover Barrachina I, Camarasa Lillo N, Bermejo-Sánchez E, Escandón Alvarez J. [Evolution of the frequency of congenital defects in newborn infants and fetuses from terminations of pregnancy after prenatal diagnosis in the period 1982-2009]. Med Clin (Barc). 2013 Aug 17;141(4):152-8. PMID: 22841468. doi: 10.1016/j.medcli.2012.05.021. Epub 2012 Jul 28. Spanish.

Highlights

- ECEMC's Clinical Network (Spanish Collaborative Study of Congenital Malformations) (more than 400 physicians from all over Spain).
- Clinical-dysmorphologic assessment of 850 newborn infants with congenital defects (CD) in Spain.
- Cytogenetic studies (high-resolution and molecular): 225 samples in ECEMC's frame.
- 474 consultations from physicians to SITTE (Spanish Teratology Information Service by Phone).
- 3,737 consultations to SITE (Phone Information Service for Pregnant Women).
- Epidemiological Surveillance of CD in Spain.
- European Surveillance of CD in EUROCAT (www.eurocat-network.eu)
- World epidemiological surveillance of CD in ICBDSR (www.icbdsr.org)
- "EUROCAT Joint Action (2011-2013)", EAHC, EU Health Programme 2008-2013. PI: Helen Dolk. Ref.2010 22 04.
- Project: "Clinical and etiological research on congenital atypical craniofacial clefts (CACFC)". PI: E. Bermejo-Sánchez. PI12/00759.
- Agreement ISCIII-ASEREMAC 2013. "Research on the clinical-etiological and epidemiological aspects of the infants born with malformations and oter CD". PI: M.L. Martínez-Frías.
- Agreements ASEREMAC-Health Administration of different Autonomous Communities. "Clinica, epidemiological, cytogenetic and teratological research on infants with malformations and other CD". PI: M.L. Martínez-Frías.
- Vice-Chair of ICBDSR's Executive Committee.
- Participation in ENTIS (http://www.entis-org.eu/) and OTIS (https://www.mothertobaby.org).
- Clinical guidances: Publication of 6 "Propositus".
- Edición del "Boletín del ECEMC: Revista de Dismorfología y Epidemiología" VI, 2 (2012) (http://revistas.isciii.es/revistas.jsp?id=ECEMC).
- Teaching at Master Early Attention (Málaga) and Oficial Master "Current knowledge on Rare Diseases". Universidad Internacional de Andalucía.
- Organization of:
  - "XXXVI ECEMC's Annual Meeting" and "Up-date Course on the research of CD". Estepona. 2.2 credits CFCPS Comunidad de Madrid-SNS. Ref.13/7653.
  - "Conference on Dysmorphology. Definition of the different concepts and their utility for clinical practice in the molecular era". 0.7 credits CFCPS Comunidad de Madrid-SNS. Ref.13/9556). ENS, Madrid.
  - "40th Annual Meeting ICBDSR". San José (Costa Rica)

PROGRAMME:
Medicina Pediátrica y del Desarrollo

Group U726

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Main lines of research

- Mental retardation of genetic origin.
- Familial cutaneous melanoma.
- Genodermatosis.
- Autism.
- Fragile X síndrome.

Most relevant scientific articles

- Iles MM. et al. GenoMEL Consortium; Q-MEGA and AMFS Investigators. A variant in FTO shows association with melanoma risk not due to BMI. Nat Genet. 2013 Apr;45(4):428-32, 432e1. IF: 35.209.
- Puig-Butille JA, Escámez MJ, García-García F, Tell-Marti G, Fabra A, Martínez-Santamaría L, Badenas C, Aguilera P, Pevida M, Dopazo J, Del Río M, Puig S. Capturing the biological impact of CDKN2A and MC1R genes as an early predisposing event in melanoma and non melanoma skin cancer. Oncotarget. 2013 Dec 16. [Epub ahead of print] IF: 6.636.
- Silva F, Rodríguez-Revenga L, Madrigal I, Alvarez-Mora MI, Oliva R, Milà M. High apolipoprotein E4 allele frequency in FXTAS patients. Genet Med. 2013 Aug;15(8):639-42. IF: 5.56.
- Brea-Fernández A, Cameselle-Teijeiro J, Alenda C, Fernández-Rozadilla C, Cubiella J, Clofent J, Reñé J, Anido U, Milá M, Balaguer F, Castells A, Castellvi-Bel S, Jover R, Carracedo A, Ruiz-Ponte C. High incidence of large deletions in the PMS2 gene in Spanish Lynch syndrome families. Clin Genet. 2013 Jul 9. doi: 10.1111/cge.12232. [Epub ahead of print] IF: 4.247.
- Alvarez-Mora MI, Rodríguez-Revenga L, Madrigal I, Torres-Silva F, Mateu-Huertas E, Lizano E, Friedländer MR, Martí E, Estivill X, Milà M. MicroRNA expression profiling in blood from fragile X-associated tremor/ataxia syndrome patients. Genes Brain Behav. 2013 Aug;12(6):595-603. IF: 3.597.

Highlights

During 2013, the group has published 26 original articles related to: FMR1 premutation associated pathologies, intellectual disabilities, genetics basis of familial melanoma and other genodermatosis; it has also been published Fragile-X Syndrome clinical guidelines ("Clinical guideline of gene FMR1-associated diseases: fragile X syndrome, primary ovarian insufficiency and tremor-ataxia syndrome."). By other hand, the group has organized 2 international meetings:

- European Organization for Research and Treatment of Cancer- EORTC (Palma de Mallorca, 12-14th September 2013)
- Intellectual Disabilities: diagnostic challenges in array CGH and next generation sequencing studies (Barcelona, 3-4th October 2013)

The group has obtained 5 competitive projects:

- "DIAGNOPTICS— Diagnosis of skin cancer using optics"(CIP-ICT-PSP-2013-7; COMPETITIVENESS AND INNOVATION FRAMEWORK PROGRAMME(CIP).
- "Study of the oxidative stress pathway and mitochondrial dysfunction in FXTAS patients. Searching for a specific biomarker that allows presymptomatic diagnosis and prognosis of the disease." (PI12/00879, ISCIII).
- "Using genome homozygous regions for identification of prognostic genes in melanoma and the development of a molecular prognostic panel (PI12/00840, ISCIII).
- "Implementation of personalized medicine based on genetic susceptibility and molecular signatures in the tumor in cutaneous melanoma: identification of new targets for the treatment of melanoma (Num: 20133134, La Marató TV3)
- "Identification of novel pathophysiological mechanisms in Kindler Syndrome" (13-726/142.04, CiberER-ISCIII)

It has began the clinical trial NCT01855971 (phase II) "Estrogen Receptors Beta (ER-B) as Therapeutic Targets for the Improvement of Cognitive Performance in Fragile-X (TESXF)." Fragile X Foundation USA.

Finally, during 2013 the group has carried out the molecular characterization of variants obtained by whole exome sequencing in families affected with intellectual disability, familial melanoma and other genodermatoses (ej.Phacomatosis Pigmentovascularis).

PROGRAMME:
Mitochondrial Medicine

Group U727

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Main lines of research

- Genetic and molecular diagnosis of mitochondrial DNA disorders and study of the physiopathogenic mechanism of mutations.
- Study of mtDNA population genetic variants conferring susceptibility to multifactorial diseases.
- Characterization of environmental factors interacting with the genetic pool in susceptibility development.
- Search of drugs acting on the OXPHOS system.
- Human chronic fatigue and pain syndromes.
- Use of dtam cell as a model for he study of Physiopatologic mechanism of thr new mutations in the mitochondrial DNA.
- mtDNA variation and neurodegenerative diseases.
- Improvement of the model of cybrids for the study of pathological mutations.

Most relevant scientific articles

- Pacheu-Grau, D., Gomez-Duran, A., Iglesias, E., López-Gallardo, E., Montoya, J., Ruiz-Pesini, E. "Mitochondrial antibiograms in personalized medicine". Hum Mol Genet. 22, 1132-1139, 2013.
- Llobet, L., Gómez-Durán, A., Iceta, R., Iglesias, E., Montoya, J., Martín-Martínez, J., Ara, J. R., Ruiz-Pesini, E. "Stressed cybrids model demyelinated axons in multiple sclerosis". Metabolic Brain Disease 28, 639–645, 2013.
- Montero, R., Grazina, M., López-Gallardo, E., Montoya, J., Briones, P., Navarro-Sastre, A., Land, J. M., Hargreaves, I. P., Artuch, R. "Coenzyme Q deficiency in mitochondrial DNA depletion síndromes". Mitochondrion 13, 337–341, 2013.
- Lorente, L., Iceta, R., Martín, M. M., López-Gallardo, E., Solé-Violán, J., Blanquer, J., Labarta, L., Díaz, C., Borreguero-León, J. M., Jiménez, A., Montoya, J., Ruiz-Pesini, E. "Severe septic patients from mitochondrial DNA haplogroup JT show higher survival rates: A multicenter, observational and prospective study". PLoS ONE. 8 (9), e73320, 2013. (doi: 10.1371/journal.pone.0073320).
- Palacín, M., Coto, E., Llobet, L, Pacheu-Grau, D., Montoya, J., and Ruiz-Pesini, E. "FK506 affects mitochondrial protein synthesis and oxygen consumption in human cells". Cell Biology and Toxicology. 29, 407-414, 2013.

Highlights

Molecular-Genetic diagnosis of mitochondrial DNA diseases. Construction of transmitochondrial cybrids that can differentiate into neurons for the study of the physiopathogenic mechanism of newmutations. Study of the population mtDNA genetic variants which cause sensitivity to multifactorial diseases. Characterisation of environmental and nuclear-genetic factors interacting with the genetic background in the development of susceptibility to diseases. Search for drugs acting at the OXPHOS system level. Chronic human pain and fatigue

RESEARCH GRANTS.

- Eduardo Ruiz Pesini. "Toxicogenomics of the oxidative phosphorylation system in Parkinson disease". Instituto de Salud Carlos III. Fondo de Investigación Sanitaria PI11/01301 Duración: 2012-2014
- Julio Montoya Villarroya. "New mitochondrial DNA mutations associated to diseases: Characterization in transmitochondrial cybrids built with immortalized cellular lines and human adult stem cells". Instituto de Salud Carlos III. Fondo de Investigación SanitariaPI10/00662 Duración: 2011-2014 (Intrasalud)

DEFENDED PHD THESIS.

- "Mitochondrial DNA mutations associated to diseases: respiratory chain complex IV deficit and other alteratios" otras alteraciones". María Dolores Herrero Martín, Universidad de Zaragoza. July 12th, 2013. Qualification: Apto "cum laude"

CONFERENCIES.

- Son Espases Hospital. Palma de Mallorca. January 30, 2013. "Genetics of the mitochondrial diseases"
- Asociación de Enfermos de Patología Mitocondrial. Madrid. October 26, 2013. "Genetic therapy of hereditary mitochondrial DNA diseases"
- CREER (National centre for Rare Diseases. Burgos. Noviembre 13, 2013. "Cellular models for the study of the patogeneicity of new mitochondrial DNA mutations and of possible therapeutic compounds"

PROGRAMME:
Sensorineural Pathology

Group U728

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Main lines of research

- Hereditary (syndromic and non-syndromic) hearing loss: identification of new genes, genetic epidemiology by means of OMIC approaches (NGS and aCGH), functional studies and generation of murine models.
- Hereditary basis for glaucoma and for the pathology of anterior segment of the eye.
- Hidradenitis suppurativa: identification of the genes responsible for it, genetic epidemiology and functional studies.
- SAPHO syndrome (chronic recurrent multifocal osteomyelitis): identification of the gene responsible for it.
- Neurofibromatosis type 1 and 2 and neuro-cardio-facial-cutaneous syndromes.
- Spinal muscular atrophy.
- microRNA cure: Modulation of microRNAs to eliminate latency reservoirs in HIV patients.
- Genetic-molecular basis for Chiari syndrome.
- Study of primary immunodeficiencies associated with the TCR/CD3 complex and with DNA repair defects.

Most relevant scientific articles

- Legan PK, Goodyear RJ, Morín M, Mencia A, Pollard H, Olavarrieta L, Korchagina J, Modamio-Hoybjor S, Mayo F, Moreno F, Moreno-Pelayo MA, Richardson GP.Three deaf mice: mouse models for TECTA-based human hereditary deafness reveal domain-specific structural phenotypes in the tectorial membrane.Hum Mol Genet. 2014 May 15;23(10):2551-68.
- Schraders M, Ruiz-Palmero L, Kalay E, Oostrik J, del Castillo FJ, Sezgin O, Beynon AJ, Strom TM, Pennings RJ, Seco CZ, Oonk AM, Kunst HP, Domínguez-Ruiz M, García-Arumi AM, del Campo M, Villamar M, Hoefsloot LH, Moreno F, Admiraal RJ, del Castillo I, Kremer H. Mutations of the gene encoding otogelin are a cause of autosomal-recessive nonsyndromic moderate hearing impairment. Am J Hum Genet. 2012 Nov 2;91(5):883-9.
- Heidenreich M, Lechner SG, Vardanyan V, Wetzel C, Cremers CW, De Leenheer EM, Aránguez G, Moreno-Pelayo MA, Jentsch TJ, Lewin GR. KCNQ4 K+ channels tune mechanoreceptors for normal touch sensation in mouse and man. Nature Neurosci, 15:138-145 (2011).
- Morin M, Bryan KE, Mayo-Merino, F, Goodyear R, Mencia A, Modamio-Hoybjor S, del Castillo I, Cabalka JM, Richardson G, Moreno F, Rubenstein PA, Moreno-Pelayo MA. In vivo and in vitro effects of two novel gamma actin (ACTG1) mutations that cause DFNA20/26 hearing impairment. Hum Mol Genet, 18: 3075-3089 (2009).
- Mencía A, Modamio-Høybjør S, Redshaw N, Morín M, Mayo-Merino F, Olavarrieta L, Aguirre LA, del Castillo I, Steel KP, Dalmay T, Moreno F, Moreno-Pelayo MA. Mutations in the seed region of human miR96 are responsible for non-syndromic progressive hearing loss. Nature Genet, 41:609-613 (2009).
- Lewis M, Quint E, Glazier A, Fuchs H, Hrabé de Angelis M, Langford C, Van Dongen S, Abreu-Goodger C, Piipari M, Redshaw N, Dalmay T, Moreno Pelayo MA, Anton J Enright. AJ & Steel KP. An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. Nature Genet, 41:614-618 (2009).

Highlights

The U728 has focused his research in the last 20 years in different genetically based diseases such as neurofibromatosis , spinal muscular atrophy and sensorineural disorders like hereditary deafness and anterior segment of the eye. Hereditary hearing loss is characterized by high genetic heterogeneity and is one of the most active research lines have been developed in recent years with numerous achievements in the field of translational research, innovation and transfer market. In 2013 these lines of research are being funded research projects for 7 (FIS , Fundación Ramón Areces , the International Cooperation Project , CNPq - Brazil) that have led to 7 publications in first-quartile international journals and 19 communications to congress, 9 of them at international conferences. In the field of knowledge transfer, we have signed four licenses for commercial use of diagnostic tools based on new generation technologies (aCGH and NGS) for hearing loss that have been designed and validated in our laboratory. In turn we have published a clinical guideline " EMQN Best Practice guidelines for diagnostic testing of non - Causing mutations syndromic hearing impairment at the DFNB1 locus " field diagnosis of hereditary hearing impairment .

Our laboratory in 2013 has been co-organizer of the XXVII Congress of the National Association of Human Genetics held in Madrid and member of the organizing committee of the 50th Workshop on Inner Ear Biology Alcalá de Henares.

PROGRAMME:
Mitochondrial Medicine

Group U729

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Main lines of research

- Mitochondrial diseases due to coenzyme Q deficiencies.
- Mechanisms of regulation of coenzyme Q biosynthesis.
- Molecular structure of CoQ biosynthesis complex and its role in secondary deficiency.
- Other lines extramitochondrial:
  - Metabolism and aging
  - Epigenetic changes induced by both nutritional interventions and exercise.

Most relevant scientific articles

- Martín-Montalvo A, González-Mariscal I, Pomares-Viciana T, Padilla-López S, Ballesteros M, Vazquez-Fonseca L, Gandolfo P, Brautigan DL, Navas P, Santos-Ocaña C. The phosphatase Ptc7 induces coenzyme Q biosynthesis by activating the hydroxylase Coq7 in yeast. J Biol Chem. 288(39):28126-37 (2013).
- Lapuente-Brun E, Moreno-Loshuertos R, Acín-Pérez R, Latorre-Pellicer A, Colás C, Balsa E, Perales-Clemente E, Quirós PM, Calvo E, Rodríguez-Hernández MA, Navas P, Cruz R, Carracedo Á, López-Otín C, Pérez-Martos A, Fernández-Silva P, Fernández-Vizarra E, Enríquez JA. Supercomplex assembly determines electron flux in the mitochondrial electron transport chain. Science 340(6140):1567-70 (2013).
- Montero R, Grazina M, López-Gallardo E, Montoya J, Briones P, Navarro-Sastre A, Land JM, Hargreaves IP, Artuch R; O'Callaghan MM, Jou, C, Jimenez C, Buján N, Pineda M, García-Cazorla A, Nascimento A, Perez-Dueñas B, Ruiz-Pesini E, Fratter C, Salviati L, Simões M, Mendes C, JoäoSantos M, Diogo L, García P, Navas P. Coenzyme Q_{10} deficiency in mitochondrial DNA depletion syndromes. Mitochondrion 13(4):337-41 (2013).
- Fernández-Ayala DJ, Guerra I, Jiménez-Gancedo S, Cascajo MV, Gavilán A, Dimauro S, Hirano M, Briones P, Artuch R, de Cabo R, Salviati L, Navas P. Survival transcriptome in the coenzyme Q10 deficiency syndrome is acquired by epigenetic modifications: a modelling study for human coenzyme Q10 deficiencies. BMJ 3(3). pii: e0025242013.
- Jimenez-Gomez Y, Mattison JA, Pearson KJ, Martín-Montalvo A, Palacios HH, Sossong AM, Ward TM, Younts CM, Lewis K, Allard JS, Longo DL, Belman JP, Malagon MM, Navas P, Sanghvi M, Moaddel R, Tilmont EM, Herbert RL, Morrell CH, Egan JM, Baur JA, Ferrucci L, Bogan JS, Bernier M, de Cabo R. Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet. Cell Metab. 18(4):533-45 (2013).

Highlights

BIOCHEMICAL/MOLECULAR DIAGNOSIS. The research group U729 has maintained our translational activity through our service to both public and private Andalussian hospitals for the diagnostics of mitochondrial pathologies. We receive biopsies on mondays that were prescribed by mainly neuropediatricians in which we analyze both electron chain complexes activities and the content of coenzyme Q10. In positive cases, we receive a skin biopsy to try molecular diagnosis. In 2013 we did the analysis of 250 biopsies.

PROJECTS. During 32013 we participated in the application for three projects that were funded. The two firsts corresponded to the 2012 call but were initiated in 2013, and the third one was approved in 2013 and started this year.

- Coenzyme Q10 deficiency syndrome: understanding the genotype-phenotype association and metabolic dysfunction through generation of induced pluripotent stem cells (ipscs) from patient-specific uncorrected and genetically-corrected cells. ERANET-RARE 2012 (2013-2015) PI: Pablo Menéndez.
- Utilización de células madre pluripotentes inducidas (iPS) para el estudio y tratamiento de enfermedades mitocondriales. CIBERER ACCI 2012 (2013-2014) PI: Rafael Garesse.
- Terapia del síndrome de deficiencia de CoQ10. Junta de Andalucía-Proyectos de Excelencia CTS 943 PI: Plácido Navas

RESULTS

- We have demonstrated that the different levels of mtDNA are related to the changes in the activities of respiratory chain and leads to a secondary deficiency of CoQ10.
- We have developed a ADCK2 KO mouse that mimic the pathology of the fatty acids metabolism observed in patients with a heterozygotic mutation in these gene.
- We have obtained induced pluripotent stem cells (iPSCs) from fibroblasts of a patient with a mutation in COQ4 to study its role in motoneuron differentiation.

PROGRAMME:
Inherited Metabolic Medicine

Group U730

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Main lines of research

- Heteromeric aminoacid transporters (cystinuria and lysinuria).
- Mitochondrial genetics (at the present, also prostate cancer).
- Knockout model for megalencephalic leukoencephalopathy (MLC1).
- Molecular study of Wolfram Syndrome.
- News biochemical and genetis essays to identify MLC1 interactome.
- Characterization of the knockout mouse for LAT-2 transporter.
- Generation and characterization of the double LAT-2/Tat1 knockout mouse.

Most relevant scientific articles

- Differential cystine and dibasic amino acid handling after loss of function of the amino acid transporter b0,+AT (Slc7a9) in mice. Di Giacopo A, Rubio-Aliaga I, Cantone A, Artunc F, Rexhepaj R, Frey-Wagner I, Font-Llitjós M, Gehring N, Stange G, Jaenecke I, Mohebbi N, Closs EI, Palacín M, Nunes V, Daniel H, Lang F, Capasso G, Wagner CA. Am J Physiol Renal Physiol. 2013 Dec 15;305(12):F1645-55. doi: 10.1152/ajprenal.00221.2013. Epub 2013 Oct 9.
- EURO-WABB: an EU rare diseases registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome. Farmer A, Aymé S, de Heredia ML, Maffei P, McCafferty S, Młynarski W, Nunes V, Parkinson K, Paquis-Flucklinger V, Rohayem J, Sinnott R, Tillmann V, Tranebjaerg L, Barrett TG. BMC Pediatr. 2013 Aug 27;13:130. doi: 10.1186/1471-2431-13-130.
- Insights into MLC pathogenesis: GlialCAM is an MLC1 chaperone required for proper activation of volume-regulated anion currents. Capdevila-Nortes X, López-Hernández T, Apaja PM, López de Heredia M, Sirisi S, Callejo G, Arnedo T, Nunes V, Lukacs GL, Gasull X, Estévez R. Hum Mol Genet. 2013 Nov 1;22(21):4405-16. doi: 10.1093/hmg/ddt290. Epub 2013 Jun 20.
- Protein kinase CK2-dependent phosphorylation of the human Regulators of Calcineurin reveals a novel mechanism regulating the calcineurin-NFATc signaling pathway. Martínez-Høyer S, Aranguren-Ibáñez A, García-García J, Serrano-Candelas E, Vilardell J, Nunes V, Aguado F, Oliva B, Itarte E, Pérez-Riba M. Biochim Biophys Acta. 2013 Oct;1833(10):2311-21. doi: 10.1016/j.bbamcr.2013.05.021. Epub 2013 Jun 1.
- Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. de Heredia ML, Clèries R, Nunes V. Genet Med. 2013 Jul;15(7):497-506. doi: 10.1038/gim.2012.180. Epub 2013 Feb 21.

Highlights

During 2013, the team has obtained a new project, FIS: PI13/00121, has initiated the project from ELA foundation 2012-014C2B, and kept on working on the EUROWABB (EAHC- 20101215) and SGR projects (SGR 2009-1490). It has also participated in the exome sequence project within the CIBERER.

The group main topics are:

- Wolfram Syndrome: During 2013 we published a clinical-genetic association analysis on 400 patients which proposes a new patient classification based on their genotype. We have also provided new data on the natural history of the disease. We have kept on working in the relation between symptoms and the genotypic classes assigned according to the paper. We have kept working within EURO-WABB that resulted in multiple congress communications, to the publication of clinical guidelines ant to the publication of 1 paper.
- MLC: We have published demonstrating the role of GlialCAM as MLC1 chaperone which is needed to regulate the anionic currents involved in volume regulation. We kept characterizing the KO mice model generated for this disease which has been published by beginning 2014.
- Heteromeric amino acid transporters: We have characterized the mice KO models for LAT2 and LAT2/TAT1. LAT 2 is responsible for glutamine efflux in muscle (unpublished data). We have also studied the involvement of LAT 2 and TAT1 in amino acid reabsorbtion in kidney as well as their relation with other amino acid transporters. A paper studied the mice KO b0,+AT for has been published.

CLINICAL GUIDELINES: we have participated in the clinical guidelines for Wolfram, Bardet-Biedl and Alström syndromes which have been published, within EURO-WABB project.

The group also performed genetic diagnostic in families with LPI and cystinuria for the genes SLC3A1, SLC7A9, SLC7A7.

PROGRAMME:
Inherited Metabolic Medicine

Group U731

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Main lines of research

- Structure and function of heteromeric aminoacid transporters. Physiopathology or renal reabsorption of aminoacids.

Most relevant scientific articles

- Differential cystine and dibasic amino acid handling after loss of function of the amino acid transporter b0,+AT (Slc7a9) in mice. Di Giacopo A, Rubio-Aliaga I, Cantone A, Artunc F, Rexhepaj R, Frey-Wagner I, Font-Llitjós M, Gehring N, Stange G, Jaenecke I, Mohebbi N, Closs EI, Palacín M, Nunes V, Daniel H, Lang F, Capasso G, Wagner CA. Am J Physiol Renal Physiol. 2013 Dec 15;305(12):F1645-55.
- Mfn2 modulates the UPR and mitochondrial function via repression of PERK. Muñoz JP, Ivanova S, Sánchez-Wandelmer J, Martínez-Cristóbal P, Noguera E, Sancho A, Díaz-Ramos A, Hernández-Alvarez MI, Sebastián D, Mauvezin C, Palacín M, Zorzano A. EMBO J. 2013 Aug 28;32(17):2348-61.
- The SLC3 and SLC7 families of amino acid transporters. Fotiadis D, Kanai Y, Palacín M. Mol Aspects Med. 2013 Apr-Jun;34(2-3):139-58.
- The small SLC43 family: facilitator system l amino acid transporters and the orphan EEG1. Bodoy S, Fotiadis D, Stoeger C, Kanai Y, Palacín M. Mol Aspects Med. 2013 Apr-Jun;34(2-3):638-45. doi: 10.1016/j.mam.2012.12.006.
- Expression of human heteromeric amino acid transporters in the yeast Pichia pastoris. Costa M, Rosell A, Álvarez-Marimon E, Zorzano A, Fotiadis D, Palacín M. Protein Expr Purif. 2013 Jan;87(1):35-40.

Highlights

Our most relevant result related to rare diseases during 2013 has been the generation of the first structural model of a human Heteromeric Amino acid Transporter (HAT). In 2013 we reported the expression of human HATs in the yeast Pichia (article 5 in the previous section). This was the base to obtain purified human 4F2hc/LAT2, which allowed negative-staining electron microscopy studies that rendered a model of the heterodimer at 21 Å resolution. Docking analysis and biochemical crosslinking experiments refined and confirmed the model. Our results showed that the ectodomain of the heavy subunit 4F2hc almost completely covers the external face of the light subunit and increases its stability. This model is at present the structural paradigm of two transporters (rBAT/b0,+AT and 4F2hc/y+LAT1) which mutations cause aminoacidurias (cystinurias type A and B and isolated cystinuria, and lysinuric protein intolerance; LPI). These results have been publish beginning of 2014 ((Rosell A, Meury M, Álvarez-Marimon E, Costa M, Pérez-Cano L, Zorzano A, Fernández-Recio J, Palacín M, Fotiadis D (2014) Proc Natl Acad Sci U S A. 111:2966-71). This research has been supported by EDICT (7FP.Health-2007-2.1.1-5 Grant Agreement: 201924) and SAF 2012-40080 (MICINN). Our leadership on structural studies of HATs facilitated to obtain financial support to solve the atomic structure of bacterial homologues of the transporter mutated in LPI (4F2hc/y+LAT1) (Fundación Ramón Areces and to develop 4F2hc/xCT inhibitors, a therapeutic target in gliomas (Fundació La Marató-TV3).

In a collaborative study with different CIBERER units we have obtained for the first time expression in bacteria and purification of human BCKDK, main protein controlling oxidation of branched-chain amino acids. This preparation allowed the determination of the residual kinase activity of mutants causing a new neurobehavioral deficit. This study has been published at beginning of 2014 (García-Cazorla A et al. Hum Mutat. 2014 Apr;35(4):470-7).

PROGRAMME:
Genetic Medicine

Group U732

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Main lines of research

- Genetics and molecular epidemiology of neurological rare diseases.
- Neurobiology and cellular physiopathology of mitochondrial-associated Charcot-Marie-Tooth neuropathies (CMT4A, CMT2K, CMT2A) and CMT4C, Friedreich ataxia and Duchenne muscular dystrophy.
- Animal and cellular models of genetic disorders: comparative and functional genomics of Charcot-Marie-Tooth disease and cerebellar ataxias and planar polarity biology.

Most relevant scientific articles

- Pla-Martín D, Rueda CB, Estela A, Sánchez-Piris M, González-Sánchez P, Traba J, de la Fuente S, Scorrano L, Renau-Piqueras J, Alvarez J, Satrústegui J, Palau F. Silencing of the Charcot-Marie-Tooth disease-associated gene GDAP1 induces abnormal mitochondrial distribution and affects Ca2+ homeostasis by reducing store-operated Ca2+ entry. Neurobiol Dis 2013; 55: 140-51. doi: 10.1016/j.nbd.2013.03.010. Epub 2013 Mar 28. PMID: 23542510.
- Gouttenoire EA, Lupo V, Calpena E, Bartesaghi L, Schüpfer F, Médard JJ, Maurer F, Beckmann JS, Senderek J, Palau F, Espinós C, Chrast R. Sh3tc2 deficiency affects neuregulin-1/ErbB signaling. Glia 2013l ;61: 1041-51. doi: 10.1002/glia.22493. Epub 2013 Apr 2. PMID: 23553667.
- González-Cabo P, Palau F. Mitochondrial pathophysiology in Friedreich's ataxia. J Neurochem 2013; 126 (Suppl. 1): 53-64. doi: 10.1111/jnc.12303. Review. PMID: 23859341.
- Sivera R, Sevilla T, Vílchez JJ, Martínez-Rubio D, Chumillas MJ, Vázquez JF, Muelas N, Bataller L, Millán JM, Palau F, Espinós C. Charcot-Marie-Tooth disease: genetic and clinical spectrum in a Spanish clinical series. Neurology 2013; 81: 1617-25. doi: 10.1212/WNL.0b013e3182a9f56a. Epub 2013 Sep 27. PMID: 24078732.
- Sevilla T, Martínez-Rubio D, Márquez C, Paradas C, Colomer J, Jaijo T, Millán JM, Palau F, Espinós C. Genetics of the Charcot-Marie-Tooth disease in the Spanish Gypsy population: the hereditary motor and sensory neuropathy-Russe in depth. Clin Genet 2013; 83: 565-70. doi: 10.1111/cge.12015. Epub 2012 Oct 10. PMID: 22978647.

Highlights

The group is funded by international competitive projects (FP7 ; IRDiRC/ISCIII), National (R+D + i National Plan, AES) , regional (Prometeo GV) and private foundations (Marató TV3 Foundation, A. Koplowitz Foundation and I. Gemio Foundation). Moreover we maintain a high degree of collaboration with other CIBERER groups through competitive projects (IRDiRC / ISCIII - JM Millán, J. Satrústegui , F. and JM Pallardó Cuezva ; Prometeo GV - P. Sanz and V. Rubio).

Milestones of the group are:

- Genetics and pathophysiology of Charcot- Marie -Tooth (CMT) – The genetic causes of these hereditary neuropathies by searching new CMT genes and mutations (Sivera et al. Neurology 2013) and the underlying pathogenesis of CMT forms associated with mitochondrial genes (GDAP1 and MFN2) and the demyelinating gene SH3TC2. We have found two new genes that currently are in functional validation study, and we have described the pathogenic mechanisms and cellular pathophysiology of forms AR-CMT2K/CMT4A (GDAP1) and CMT4C (SH3TC2) . The major achievements should be noted: a) confirmation of the participation of GDAP1 on mitochondrial dynamics and distribution; b) demonstration of the role of GDAP1 in the mitochondria-endoplasmic reticulum and interaction with the SOCE mechanism of calcium homeostasis in the pathogenesis of GD AP1 deficiency (Pla -Martin et al. Neurobiol Dis 2013).
- Neurobiology and cellular pathophysiology of Friedreich's ataxia (FRDA) – The study of FRDA pathophysiology in a model of FXN gene silencing in the neuroblastoma line SH-SY5Y, and in the transgenic mice YG8R (González -Cabo and Palau, J Neurochem 2013). The most important result has been the establishment of the relationship of frataxin deficiency and cellular senescence (Bolinches-Amorós et al., Front Cell Neurosci, in press).

In summary, the milestones of the group can be summarized as: (i) competitive scientific level in the field of neuromuscular diseases, (ii) cooperation with other CIBERER groups (Spanish CMT Consortium), (iii) fostering clinical translation (Genomics and Translational Genetics Service at CIPF), and (iv) international leadership in the field of rare diseases with participation in the EUCERD committee and European projects (EFACTS, EUCERD Joint Action, Orphanet).

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U733

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Main lines of research

- Physiopathology of oxidative stress in Fanconi anemia and Friedreich ataxia.
- Kindler's syndrome fibroblast oxidative profile.
- Cell cycle regulation in Down syndrome.
- Epigenetics in rare diseases.

* At the expense of Project

Most relevant scientific articles

- García-Giménez JL, Seco-Cervera M, Aguado C, Romá-Mateo C, Dasí F, Priego S, Markovic J, Knecht E, Sanz P, Pallardó FV. Lafora disease fibroblasts exemplify the molecular interdependence between thioredoxin 1 and the proteasome in mammalian cells. Free Radic Biol Med 2013; 2013 Jul 9. [Epub ahead of print].
- Pagano G, Talamanca AA, Castello G, d'Ischia M, Pallardó FV, Petrovic S, Porto B, Tiano L, Zatterale A. Bone marrow cell transcripts from Fanconi anaemia patients reveal in vivo alterations in mitochondrial, redox and DNA repair pathways. Eur J Haematol 2013; 2013 Aug. 91(2):141-51.
- Sandoval J, Peiró-Chova L, Pallardó FV, García-Giménez JL. Epigenetic biomarkers in laboratory diagnostics: emerging approaches and opportunities. Expert Rev Mol Diagn 2013; 2013 Jun. 13(5):457-71.
- Pagano G, Talamanca AA, Castello G, d'Ischia M, Pallardó FV, Petrovic S, Porto B, Tiano L, Zatterale A. From clinical description to in vitro and animal studies, and backwards to patients: Oxidative stress and mitochondrial dysfunction in Fanconi anaemia. Free Radic Biol Med 2013; 2013 Jan 29. [Epub ahead of print].
- García-Giménez JL, Olaso G, Hake S, Bönisch C, Wiedemann S, Markovic J, Dasi F, Gimeno A, Perez-Quilis C, Capdevila M, Palacios O, Vina J, Pallardo F. Histone H3 glutathionylation in proliferating mammalian cells destabilizes nucleosomal structure. Antioxid Redox Signal 2013; 2013 Mar 31. [Epub ahead of print].

Highlights

- Saving Live at Birth. Belinda and Bill Gates foundation & USAID and Grand Challenges Canada. Washington, July 2013. Funding of the international project entitled: "HIST-BIRTH: Innovative and rapid point of-care histone test strips for early diagnosis of sepsis in pregnancy and childbirth", an international joint project where the principal investigator is Dr. F. Pallardó. Collaboration between U733/ University of Valencia, the Polytechnic University of Valencia, the International University of Kampala (Uganda) and a private company Bioarray S.L).
- Dr. José Luis García-Giménez won the national award for Young Entrepreneurs INJUVE, given by the Spanish Ministry of Health. The goal of the project awarded is the constitution of a new R&D company called "Epidisease S.L.". A Project that targets translation of the knowledge in new technologies to innovative analysis in epigenetics for the improvement of health problems.
- Organization of the course for specialized formation in the Valencian School for Health Studied (EVES). This training course is addressed to health workers of the Valencian health system. The course (28 hours) entitled: "Rare diseases: research, clinical care, and social awareness" Code: 31314601ª; DOGV: 6944 date: 16.01.2013). Speakers belong to CIBERER, Several National Reference centers, CIBERER biobank and Orphanet.
- Project funding: Study of miRNAs in patients with Friedreich's Ataxia. Diagnostic and Clinical implications. Strategic Health Action. ISCIIII. PI12/22263. Principal Investigator: Federico V. Pallardó. Dr. José Luis García Giménez has been recognized as "Investigador emergente" by the Research Health Institute INCLIVA . Funding of project entitled: "Identification of circulating histones in plasmas from patients suffering severe sepsis and septic shock". Funding of the project: "Epigenetic Factors and Adolescent Idiopathic Scoliosis" by The European Society for Spine. All biological samples of these studies have been stored at the CIBERER-Biobank and in the INCLIVA biobank.
- Approval of the Master on rare diseases of the University of Valencia-ADEIT. Director Dr. Federico V. Pallardó. Code.13721390

PROGRAMME:
Genetic Medicine

Group U734

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Main lines of research

- X-linked hyper IgM syndrome animal model generation. Preparation of mice with CD40L-/- platelets and/or vascular endothelial cells and comparative analysis with complete CD40L-/- mice.
- Molecular basis of platelet hyperreactivity associated to thrombotic processes.
- Use of lymphoblastic cell lines from Amytrophic Lateral Sclerosis (ALS), frontotemporal dementia (associated to progranuline mutations) and Alzheimer patients for a systematic study of mechanisms of cell death and survival in neurodegeneration.
- Molecular basis of hemorrhagic syndromes (Glanzmann thromboasthenia, Bernard-Soulier syndrome, FXIII deficiency).
- Function of the GPIb-IX complex in thrombin-induced platelet activation.
- Production of animal models with conditional ablation of the podocalyxin gene in several tissues.

Most relevant scientific articles

- N. Esteras, C. Alquézar, A. de la Encarnación, A. Villarejo, F. Bermejo-Pareja, Martín-Requero A. http://www.ncbi.nlm.nih.gov/pubmed/24499616. Calmodulin levels in blood cells as a potential biomarker of Alzheimer's disease. Alzheimers Res Ther. (2013) 5(6):55.
- N. Esteras, C. Alquézar, E. Bialopiotrowicz, F. Bermejo-Pareja, U. Wojda, A. Martín-Requero. Downregulation oof extracellular signal-regulated kinase ½ activity by Calmodulin KII modulatesp21(Cip1) levels and survival of immortalized lymphocytes from Alzheimer's disease patients. Neurobiol Aging (2013) 34(4):1090-100.
- C. Alquezar, N. Esteras, Ana de la Encarnación, A. Martín-Requero. Therapeutic Approaches for the treatment of frontotemporal lobar degeneration. Current Topics in Pharmacology (2013) Vol 17, 1, 85-101.
- Fernández D, Horrillo A, Alquezar C, González-Manchón C, Parrilla R, Ayuso MS [2013] Control of cell adhesion and migration by Podocalyxin. Implication of Rac1 and Cdc42. Biochem. Biophys. Res. Commun. (2013) 432(2):302-7.

Highlights

We have completed the development and phenotypic characterization of mouse models with tissue-specific CD40L deletion. Ablation of CD40L at different stages of hematopoietic development has provided important information on the pathogenesis and clinical manifestations of X-linked-hyper-IgM (ORPHA69712), rare disease due to mutations in the Cd40lg gene. Publication of this work has led to interesting collaborations with foreign groups to study other aspects of the disease.

Studies in a mouse model deficient in podocalicina (Podxl) generated in our laboratory have revealed the role of this protein in the control of vascular permeability and indicate that these animals represent an excellent tool for studying vasculitis (ORPHA52759), group of rare diseases for which there is so far no animal model genetically modified, so that the patentability of this model is being evaluated.

We have shown that CDK6/pRb can be considered as a novel theraputic target for FTLD associated to PGRN deficiency.

Since CDK6 can be epigenetically regulated, we hypothesized that the repositioning of drugs, such sodium butyrate, an inhibitor of histone deacetylases, may provide some hope for treatment of FTLD.

By studying the signaling pathways affected by PGRN deficiency, we found alterations in ERK1/2 cascade that seem to be responsible for the increased activation of CDK6. Thus, the repositioning of Selemetunib and MEK162, two ERK1/2 inhibitors already used in cancer treatment, was considered for FTLD. Both drugs were effective in restoring the normal response to serum stimulation or deprivation of PGRN-deficient cells.

In addition, we had evaluated the effect of restoring PGR levels by drugs able to increase the protein content at the transcriptional or postranslational level.

We have found alterations in calmodulin levels in non-neuronal cells and plasma of Alzheimer's disease patients, that could be useful as biomarker for the early diagnosis.

FUNDING:

- SAF2011-28603 (2012-2014) PI: A. Martín Requero
- XVI Convocatoria. Enfermedades raras. Fundación Ramón Areces (2012-2015) PI: A. Martín Requero
- BFU2010-15237 (2011-2014) PI: C. González Manchón

PROGRAMME:
Medicina Pediátrica y del Desarrollo

Group U735

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Main lines of research

- Williams syndrome. Molecular basis and pathogenic mechanisms.
- Human genome plasticity and disease susceptibility.
- Williams syndrome. Mouse model generation and analysis.
- Study of the genetic basis of autism spectrum disorders (ASD).
- Clinical and therapeutic research into medical genetics: Williams syndrome, Marfan syndrome and connectivopathies, new genomic syndromes and autism.
- Development and validation of high-throughput technology for diagnostic applications in medical genetics.

Most relevant scientific articles

- Toma C, Hervás A, Torrico B, Balmaña N, Salgado M, Maristany M, Vilella E, Aguilera F, Orejuela C, Cuscó I, del Campo M, Pérez-Jurado LA, Caballero-Andaluz R, de Diego-Otero Y, Pérez-Costillas L, Ramos-Quiroga JA, Ribasés M, Bayés M, Cormand B. Analysis of two language-related genes in autism: a case-control association study of FOXP2 and CNTNAP2. Psychiatr Res 23: 82-5 (2013).
- Makrythanasis P, van Bon B, Steehouwer M, Rodríguez-Santiago B, Simpson M, Dias P, Anderlid B, Arts P, Bhat M, Augello B, Biamino E, Bongers E, Del Campo M, Cordeiro I, Cueto-González A, Cuscó I, Deshpande C, Frysira E, Izatt L, Flores R, Galán E, Gener B, Gilissen C, Granneman S, Hoyer J, Yntema H, Kets C, Koolen D, Marcelis C, Medeira A, Micale L, Mohammed S, de Munnik S, Nordgren A, Psoni S, Reardon W, Revencu N, Roscioli T, Ruiterkamp-Versteeg M, Santos H, Schoumans J, Schuurs-Hoeijmakers J, Silengo M, Toledo L, Vendrell T, van der Burgt I, van Lier B, Zweier C, Reymond A, Trembath R, Perez-Jurado L, Dupont J, de Vries B, Brunner H, Veltman J, Merla G, Antonarakis S, Hoischen A. MLL2 mutation detection in 86 patients with Kabuki syndrome: a genotypephenotype study. Clin Genet. 84(6):539-45 (2013).
- Toma C, Hervás A, Balmaña N, Salgado M, Maristany M, Vilella E, Aguilera F, Orejuela C, Cusco I, Gallastegui F, Pérez-Jurado LA, Caballero-Andaluz R, de Diego Y, Guzmán-Álarez G, Ramos-Quiroga J-A, Ribasés M, Bayés M, Cormand B. Neurotransmitter systems and neurotrophic factors in autism: association study of 37 candidate genes suggests the involvement of DDC. World J Bio Psych. 14(7):516-27 (2013).
- Segura-Puimedon M, Borralleras C, Pérez-Jurado LA, Campuzano V. TFII-I regulates target genes in the PI-3K and TGF-beta signaling pathways through a novel DNA binding motif. Gene 25:527(2):529- 36 (2013).
- Sailani MR, Makrythanasis P, Valsesia A, Santoni F, Deutsch S, Popadin K, Borel C, Migliavacca E, Sharp AJ, Duriaux Sail G, Falconnet E, Rabionet K, Serra Juhé C, Vicari S, Laux D, Grattau Y, Dembour G, Megarbane A, Touraine R, Stora S, Kitsiou S, Fryssira H, Chatzisevastou-Loukidou C, Kanavakis E, Merla G, Bonnet D, Pérez-Jurado LA, Estivill X, Delabar JM, Antonarakis SE. The complex SNP and CNV genetic architecture of the increased risk of congenital heart defects in Down syndrome. Genome Res. 23(9):1410-21 (2013).

Highlights

In addition to maintain the productivity in our current areas of research, we have developed a novel Project addressed to unravel the contribution of novel inversions of the human genome to germ-line and somatic disease, with a recent high impact publication (AJHG, Mar 2014). Our group has obtained competitive funding for three novel projects: the first one would allow us to consolidate this novel line of research on inversions and human disease (FIS PI13/02481); the second one goes in depth into the molecular mechanisms of autism (FIS PI13/00823); and the third one will be addressed to develop novel drugs targeting specific aspect of the Williams-Beuren syndrome phenotype (Innopharma).

We have presented several communications in international meetings (platform and posters), obtaining the Henning Anderson award to the best communication at the meeting of the European Society for Pediatric Endocrinology (ESPE, Milan, 09-2013). We were also invited to deliver speeches in the Plenary Session of the Annual Meeting of the European Cytogenetics Association (Dublin, 06-2013), the Congress of the Asociación Española de Genética Humana (Madrid, 04-2013) (both on detectable clonal mosaicism), and the Human Genome Variation Meeting (Seoul, 09-2013) (on inversions). Transference activities were mostly done through our spin-off qGenomics which has developed and commercialized novel tools for genetic diagnosis, including a NGS-based method for carrier detection of all relevant recessive disorders, addressed to prospective parents and programs of gamete donation, as well as another for integrative analysis and molecular characterization of newborns after positive detection in the neonatal screening programs.

Respect to translational activities, we have reorganized mutidisciplinary clinics for several rare diseases in the Hospital del Mar de Barcelona. The clinics have been accredited by the Health Department of the Catalonian Government as Units of Clinical Expertise (UEC) for genetic diseases affecting neurocognition.

PROGRAMME:
Inherited Metabolic Medicine

Group U737

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Main lines of research

- Lysosomal and peroxisomal diseases.
- Intermediary metabolism and mitochondrial energy metabolism diseases.

Most relevant scientific articles

- Ferrer-Cortès X, Font A, Bujan N, Navarro-Sastre A, Matalonga L, Arranz JA,Riudor E, del Toro M, García-Cazorla A, Campistol J, Briones P, Ribes A, Tort F. Protein expression profiles in patients carrying NFU1 mutations. Contribution to the pathophysiology of the disease. J Inherit Metab Dis. 2013 Sep;36(5):841-847. IF: 4.05; 1er cuartil.
- Tiscornia G, Vivas EL, Matalonga L, Berniakovich I, Barragán Monasterio M, Eguizábal C, Gort L, González F, Ortiz Mellet C, García Fernández JM, Ribes A, Veiga A, Izpisua Belmonte JC. Neuronopathic Gaucher's disease: induced pluripotent stem cells for disease modelling and testing chaperone activity of small compounds. Hum Mol Genet. 2013 Feb 15;22(4):633-45. ; IF: 7.692; 1er decil.
- Delgadillo V, O'Callaghan Mdel M, Gort L, Coll MJ, Pineda M. Natural history of Sanfilippo syndrome in Spain. Orphanet J Rare Dis. 2013 Dec 6;8:189. IF: 4.315; 1er cuartil.
- van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S, Abulhoul L, Grünewald S, Anselm I, Azzouz H, Bratkovic D, de Brouwer A, Hamel B, Kleefstra T, Yntema H, Campistol J, Vilaseca MA, Cheillan D, D'Hooghe M, Diogo L, García P, Valongo C, Fonseca M, Frints S, Wilcken B, von der Haar S, Meijers-Heijboer HE, Hofstede F, Johnson D, Kant SG, Lion-Francois L, Pitelet G, Longo N, Maat-Kievit JA, Monteiro JP, Munnich A, Muntau AC, Nassogne MC, Osaka H, Ounap K, Pinard JM, Quijano-Roy S, Poggenburg I, Poplawski N, Abdul-Rahman O, Ribes A, Arias A, Yaplito-Lee J, Schulze A, Schwartz CE, Schwenger S, Soares G, Sznajer Y, Valayannopoulos V, Van Esch H, Waltz S, Wamelink MM, Pouwels PJ, Errami A, van der Knaap MS, Jakobs C, Mancini GM, Salomons GS. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. J Med Genet. 2013 Jul;50(7):463-472; IF:6.365; 1er decil.
- Tort F, Ferrer-Cortès X, Thió M, Navarro-Sastre A, Matalonga L, Quintana E, Bujan N, Arias A, García-Villoria J, Acquaviva C, Vianey-Saban C, Artuch R, García-Cazorla À,Briones P, Ribes A. Mutations in the lipoyltransferase LIPT1 gene cause a fatal disease associated with a specific lipoylation defect of the 2-ketoacid dehydrogenase complexes. Hum Mol Genet. 2014 Apr 1;23(7):1907-15. doi: 10.1093/hmg/ddt585. Epub 2013 Nov 20. PMID: 24256811; IF: 7.692; 1er decil.

Highlights

RESULTS: Inside the line of identification of genes responsible for inherited metabolic diseases it is worth to mention the identification LIPT1 gene in a patient with lactic acidemia. We have shown that the corresponding protein is responsible for the transfer of lipoic acid to the E2 subunit of 2-oxo- mitochondrial dehydrogenases , but not to the H -subunit of the glycine cleavage . This finding represented a new milestone in the understanding of the metabolic pathway of lipoic acid. It is remarkable that this work received the award for the best oral presentation at the 12th International Congress of Inborn Errors of Metabolism (ICIEM , September 2013).

PUBLICATIONS AND PROJECTS: In 2013 were made 20 publications in journals with impact factor, three were in the first decile and four in the first quartile. We have obtained three competitive projects (1 FIS and 2 European projects) and a contract with BioMarin Ltd.

TRANSLATION: The most important achievement has been the expansion of newborn screening to 22 diseases for all newborns of Catalunya. This program has incorporated Aleix Navarro-Sastre, who from 2006 was contracted CIBERER , having made its pre-and – post doctoral training in our group.

TRANSFER: We have made a patent about a compound that works by stimulating the lysosomal exocytosis.

Title: Exocytosis activating compounds. Inventors: Josep Farrera - Sinfreu , Leslie Matalonga Borrel , Laura Gort But Roberto Pascual Martínez , Antonio Ferrer Montiel, Antonia Ribes Rubio , Berta Ponsati Obiols Application No.: EP13382541.4. Priority country: Europe. Priority Data: 23/12/2013. Entity headline BCN PEPTIDES , S.A.

INTERNATIONALIZATION: Organization of the 12th International Congress of Inborn Errors of Metabolism (ICIEM, Barcelona, September 2013). The PI of the group has been co-president of the congress and the entire group has been part of the local organizing committee.

PROGRAMME:
Genetic Medicine

Group U738

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Main lines of research

- Molecular diagnostics and characterization of pathogenic mechanisms in pathologies associated with deregulation of the complement system.
- Molecular basis for Lafora disease.
- Animal models of disease and development of therapeutic strategies.

Most relevant scientific articles

- Alcorlo M., Tortajada A., Rodríguez de Córdoba S. and Llorca O. Structural basis for the stabilization of the complement alternative pathway C3 convertase by properdin. Proc Natl Acad Sci USA. 110:13504-9 (2013).
- Pickering MC., D'Agati VD., Nester C., Smith RJ., Haas M., Appel GB., Alpers CE., Bajema IM., Bedrosian C., Braun M., Doyle M., Fakhouri F., Fervenza FC., Fogo AB., Frémeaux-Bacchi V., Gale DP., Goicoechea de Jorge E., Griffin G., Harris CL., Holers VM., Johnson S., Lavin PJ., Medjeral-Thomas N., Morgan BP., Noel LH., Peters DK., Rodríguez de Córdoba S., Servais A., Sethi S., Song WC., Tamburini P., Thurman JM., Zavros M. and Cook HT. C3 Glomerulopathy: consensus report. Kidney International. 84:1079-89 (2013).
- Tortajada A., Yébenes H., Abarrategui-Garrido C., Anter J., García-Fernández JM., Martínez-Barricarte R., Alba-Domínguez M., Malik TH., Bedoya R., Cabrera Pérez R., López Trascasa M., Pickering MC., Harris CL., Sánchez-Corral P., Llorca O. and Rodríguez de Córdoba S. C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation. J Clin Invest. 123:2434-2446 (2013).
- Bresin E., Rurali E., Caprioli J., Sanchez-Corral P., Fremeaux-Bacchi V., Rodríguez de Córdoba S., Pinto S., Goodship TH., Alberti M., Ribes D., Valoti E., Remuzzi G., Noris M.; on behalf of the European Working Party on Complement Genetics in Renal Diseases. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol 24:475-486 (2013).
- Campistol JM., Arias M., Ariceta G., Blasco M., Espinosa M., Grinyó JM., Praga M., Torra R., Vilalta R. and Rodríguez de Córdoba S. An update for atypical haemolytic uraemic síndrome: diagnosis and treatment. A consensus document (Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento de consenso) Nefrología 33:27-45 (2013).

Highlights

Within the basic research activities of the group, during 2013 we have provided fundamental insights in the understanding of the pathogenic mechanisms of rare diseases associated with deregulation of the complement system describing, in a paper published in PNAS, how properdin stabilizes the convertase C3 of the alternative pathway, and in another paper, published in JCI, which is the role of the proteins related to factor H (FHRs) in C3 glomerulopathy . The relevance of this last work has merited an editorial article highlighting its importance, both for the clinic and basic research.

In parallel, we have continued our basic research activity on the molecular basis of Lafora disease using animal models. Here we generated results that delimit the etiopathogenic factors to a defect in the mechanisms of intracellular proteolysis. A report with these results, accepted for publication in Brain on November 2, 2013, will be published in 2014 and will be accompanied by an editorial article highlighting its importance.

The group has also developed a strong translational activity designing and implementing a NGS gene panel for the screening of genes associated with rare pathologies related to complement deregulation. In addition, the group has participated in the generation of clinical guidelines for the diagnosis of these pathologies and continued the management of the registry of patients with aHUS and C3G by the constitution of a working group on complement and renal pathology with the participation of clinical and basic researchers.

Regarding technology transfer, we have continued our work on the development of therapies with potential application in rare diseases related with deregulation of complement, generating a battery of monoclonal antibodies with complement inhibitory activities. One result of this activity has been the generation of a patent to protect an anti human factor B that effectively inhibits activation of the alternative complement pathway.

PROGRAMME:
Inherited Metabolic Medicine

Group U739

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Main lines of research

- Urea cycle related enzymopathologies.
- Structural biology of congenital hyperammonemias.
- Structural biology of rare diseases.

Most relevant scientific articles

- Diez-Fernández C, Martínez AI, Pekkala S, Barcelona B, Pérez-Arellano I, Guadalajara AM, Summar M, Cervera J, Rubio V. Molecular characterization of carbamoyl-phosphate synthetase (CPS1) deficiency using human recombinant CPS1 as a key tool. Hum Mutat. 2013 Aug;34(8):1149-59.
- Vitoria I, Dalmau J, Ribes C, Rausell D, García AM, López-Montiel J, Rubio V. Citrin deficiency in a Romanian child living in Spain highlights the worldwide distribution of this defect and illustrates the value of nutritional therapy. Mol Genet Metab. 2013 Sep-Oct;110(1-2):181-183.
- Gozalbo-Rovira R, Rodríguez-Díaz J, Saus J, Cervera J. Precise mapping of the Goodpasture epitope(s) using phage display, site-directed mutagenesis, and surface plasmon resonance. Kidney Int. 2013 Mar;83(3):438-445.
- Gallego del Sol F, Marina A. Structural basis of Rap phosphatase inhibition by Phr peptides. PLoS Biol. 2013;11(3):e1001511.
- Tormo-Más MÁ, Donderis J, García-Caballer M, Alt A, Mir-Sanchis I, Marina A, Penadés JR. Phage dUTPases control transfer of virulence genes by a proto-oncogenic G protein-like mechanism. Mol Cell. 2013 Mar 7;49(5):947-58.

Highlights

The group, supported by 5 grants (Spanish National Plan, Valencian Government, Alicia Koplowitz Foundation), participated in two EU projects (E-IMD/DG-SANCO; and Marie Curie network) and published 9 international journals papers, reporting the first in vitro expression system for human carbamoyl-phosphate sinthetase (CPS1), opening the way for testing the disease-causing nature of CPS1 deficiency-associated mutations; describing (colaboration with Hospital La Fe) the first case in Spain of citrin deficiency, an extremely rare condition in the western world, proving the efficacity of hyperproteic diet, which would be counterindicated in other urea cycle disorders, and highlighting the need for awareness; identifying the epitope of Goodpasture syndrome (a rare autoagressive syndrome), basing future drug development for this condition; and characterizing structurally signaling systems such as a novel one based on moonlighting by the enzyme dUTPase, with implications in colorectal non-polipose hereditary cancer and for antibacterials development (valuable for cystic fibrosis).

Jointly with two other CIBERER groups and UCD and E-IMD American and European consortia, we co-organized the 4th international Symposium on Urea Cycle Disorders (Barcelona, 1-3 Septiembre, 2013), and delivered an oral major talk. We brought three panels to the International Congress on Inherited Errors of Metabolism (ICIEM2013). V.Rubio was professor in the SHARE Symposium (Amsterdam; Orphan Europe) for training on hyperammonemia. Co-author of two chapters of the book "Diagnóstico y tratamiento de las enfermedades metabólicas hereditarias" (Sanjurjo/Balldellou/Ugarte eds; editorial Ergon) and, with J.Häberle, of the chapter "Hyperammonemias and related disorders" of the "Physician's Guide to the Diagnosis, Treatment and Follow-Up of Inherited Metabolic Diseases" (Blau/Duran/Gibson/Dionisi-Vici,eds.; de Springer). Both books will appear in 2014. The European Guideline on Urea Cycle Diseases (2012; V. Rubio was an autor) has based the guíde for professionals and the leaflets for patients (we collaborated in the spanish version) found in the E-IMD page (www.e-imd.org).

PROGRAMME:
Inherited Metabolic Medicine

Group U740

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Main lines of research

- Inherited metabolic diseases.
- Inherited renal diseases.

Most relevant scientific articles

- García-Gómez S, Reyes A, Martínez-Jiménez MI, Chocrón ES, Mourón S, Terrados G, Powell C, Salido E, Méndez J, Holt IJ, Blanco L. PrimPol, an archaic primase/polymerase operating in human cells. Mol Cell. 2013 Nov 21;52(4):541-53. doi: 10.1016/j.molcel.2013.09.025. Epub 2013 Oct 24. PubMed PMID: 24207056; PubMed Central PMCID: PMC3899013.
- Mesa-Torres N, Fabelo-Rosa I, Riverol D, Yunta C, Albert A, Salido E, Pey AL. The role of protein denaturation energetics and molecular chaperones in the aggregation and mistargeting of mutants causing primary hyperoxaluria type I. PLoS One. 2013 Aug 27;8(8):e71963. doi: 10.1371/journal.pone.0071963. eCollection 2013. PubMed PMID: 24205397; PubMed Central PMCID: PMC3796444.
- Pey AL, Albert A, Salido E. Protein homeostasis defects of alanine-glyoxylate amino-transferase: new therapeutic strategies in primary hyperoxaluria type I. Biomed Res Int. 2013;2013:687658. doi: 10.1155/2013/687658. Epub 2013 Jul 16. Review. PubMed PMID: 23956997; PubMed Central PMCID: PMC3730394.
- Hernández-Guerra M, de Ganzo ZA, González-Méndez Y, Salido E, Abreu P, Moreno M, Felipe V, Abrante B, Quintero E. Chronic intermittent hypoxia aggravates intrahepatic endothelial dysfunction in cirrhotic rats. Hepatology. 2013 Apr;57(4):1564-74. doi: 10.1002/hep.26152. PubMed PMID: 23174804.
- Beck BB, Baasner A, Buescher A, Habbig S, Reintjes N, Kemper MJ, Sikora P, Mache C, Pohl M, Stahl M, Toenshoff B, Pape L, Fehrenbach H, Jacob DE, Grohe B, Wolf MT, Nürnberg G, Yigit G, Salido EC, Hoppe B. Novel findings in patients with primary hyperoxaluria type III and implications for advanced molecular testing strategies. Eur J Hum Genet. 2013 Feb;21(2):162-72. doi: 10.1038/ejhg.2012.139. Epub 2012 Jul 11. PubMed PMID: 22781098.

Highlights

We are a small group, very focussed on a single topic: inborn errors of glyoxylate metabolism, financed by a single grant: SAF2011-23933.

Our most relevant contributions have been on molecular therapies for primary hyperoxaluria (PH) using mouse models developed by us. We have also used our experimental pathology expertise in fruitful collaborations with other groups working on DNA polymerases and liver disease. During 2013, we have achieved a deeper understanding of the protein homeostasis defects involved in PH type I as a basis for rational therapeutic approaches with pharmacochaperones. We have also tested the potential of cell therapy as a bridge solution for patients at high risk of death due to primary hyperoxaluria. In addition, we have developed novel mouse models to identify safe and efficient targets for substrate reduction therapy in PH.

We are also a national and partly international (Latin America and North Africa) referral center for the diagnosis and clinical advice of inborn errors of glyoxylate metabolism. During 2013, we have diagnosed and/or adviced on 16 clinical cases for these rare diseases.

We serve in international committees for the study of PH, including the scientific advisory board of patient associations such as the Oxalosis and Hyperoxaluria Foundation and the Asociación Española para el Estudio de las Glucogenosis.

PROGRAMME:
Inherited Metabolic Medicine

Group U741

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Main lines of research

- Development of bioinformatics tools for automated capture of biological information
- Modeling of metabolic networks and macromolecular structure and dynamics.
- Genomic and proteomic approaches.
- Search and characterization of angiogenesis modulators.

Most relevant scientific articles

- Alfonso P, Andreu V, Pino-Angeles A, Moya-García AA, García-Moreno MI, Rodríguez-Rey JC, Sánchez-Jiménez F, Pocoví M, Ortiz Mellet C, García Fernández JM, Giraldo P. Bicyclic derivatives of L-idonojirimycin as pharmacological chaperones for neuronopathic forms of Gaucher disease. ChemBiochem. 2013 May 27;14(8):943-9. doi: 10.1002/cbic.201200708. PMID: 23606264.
- García-Caballero M, Marí-Beffa M, Cañedo L, Medina MÁ, Quesada AR. Toluquinol, a marine fungus metabolite, is a new angiosuppresor that interferes with the Akt pathway. Biochem Pharmacol. 2013 Jun 15;85(12):1727-40. PMID: 23603293.
- Moya-García AA, Ranea JA. Insights into polypharmacology from drug-domain associations. Bioinformatics. 2013 Aug 15;29(16):1934-7. doi: 10.1093/bioinformatics/btt321. PMID: 23740740.
- Reyes-Palomares A, Rodríguez-López R, Ranea JA, Sánchez Jiménez F, Medina MA. Global analysis of the human pathophenotypic similarity gene network merges disease module components. PLoS One. 2013;8(2):e56653. doi: 10.1371/journal.pone.0056653. PMID: 23437198.
- Sánchez-Jiménez F, Ruiz-Pérez MV, Urdiales JL, Medina MA. Pharmacological potential of biogenic amine-polyamine interactions beyond neurotransmission. Br J Pharmacol. 2013 Sep;170(1):4-16. doi: 10.1111/bph.12109. PMID: 23347064.

Highlights

The CIBERER unit 741 belongs to the área of "Medidina Metabólica Hereditaria" and to the CIBERER Bioinformatic Platform (BIER). With respect to internal collaborative work, it is worth mentioning the collaborative work (U741-U752) published in ChemBioChem (2013) on the development of a potential pharmacological chaperone against Gaucher's disease, previously patented. As BIER members, we developed PhenUMA, an on-line free platform to build integrative networks on gene-phenotype-diseases relationships (www.phenuma.uma.es), It is being used by an increasing number of basic and clinic groups inside and outside CIBERER. A tutorial workshop for PhenUMA was also organized. Their authors have been awarded by Andalusia government for this initiative and its development. In relation with these activities we have contributed to several scientific meetings.

Thirteen publications were dated during 2013 with impact factor average over 4, most of them being in the first 25% of the ranking of different biomedical JCR areas and related to orphan diseases. Two european patents are dated 2013 (priority date), EP13382130.6 and EP13382284.1, under explotaitation by Instituto Biomar S.A. and Drugs Discovery S.L., respectively. Both of them are protecting potential angiogenesis modulators.

At present, the team is awarded by 3 regional grants, another 3 National Health Program Grants (mainly including specific aims on orphan diseases). We are also involved in two european networks and keep two contracts with private companies, both related to orphan diseases.

Two PhD has been defended during 2013 in relation to U741 activities (Melisa García-Caballero y María Victoria Ruiz-Pérez). Their results are interesting for orphan diseases related to angiogenesis and for low prevalent tumors as, for instance, pediatric neuroblastomas.

Our results were communicated in more than 10 Congresses (in more than 5 occasions as invited/selected speakers). In addition, we have participated in different activities of training, promotion and diffusion of biocomputational solutions applied to orphan diseases.

PROGRAMME:
Genetic Medicine

Group U742

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Main lines of research

- Lafora disease molecular basis.
- Molecular mechanisms of laforin and maline actions.
- Implication of AMP-activated kinase (AMPK) in metabolic regulation.
- Implication of type PP1 phosphatase in metabolic regulation.
- Structure and function of glucokinase and its repercussion on metabolic regulation.

* At the expense of Project

Most relevant scientific articles

- Gentry, M.S., Romá-Mateo, C., Sanz, P. "Laforin, a protein with many faces: glucan phosphatase, adaptor protein, et alii". FEBS Journal, 280, 525-537 (2013).
- Rubio-Villena, C., García-Gimeno, M.A. and Sanz, P. "Glycogenic activity of R6, a protein phosphatase 1 regulatory subunit, is modulated by the laforin-malin complex". Int. J. Biochem. Cell Biol. 45, 1479-1488 (2013).
- Rubio, T., Vernia, S. and Sanz, P. "Sumoylation of AMPKb2 subunit enhances AMP-activated protein kinase activity". Mol. Biol. Cell. 24, 1801-1811 (2013).
- Sanchez-Martín, P., Raththagala, M., Bridges, TM., Husodo, S., Gentry, M.S., Sanz, P. and Roma-Mateo, C. "Dimerization of the glucan phosphatase laforin requires the participation of Cystein 329". PLoS ONE. 8, e69523 (2013).
- García-Gimenez, J.L., Seco-Cervera, M., Aguado, C., Romá-Mateo, C., Dasi, F., Priego, S., Markovic, J., Knecht, E., Sanz, P., Pallardó, F.V. "Lafora disease fibroblasts exemplify the molecular interdependence between thioredoxin 1 and the proteasome in mammalian cells. Free Rad. Biol. Med. 65, 347-359 (2013).

Highlights

- We have confirmed that residue Cys329 in laforin is essential for the dimerization of the protein. In the absence of this residue either by mutation (C329S) or by deletion (C329X) a laforin form that is unable to dimerize is obtained. These results open a door to study the role of the laforin dimerization in cell physiology [Sanchez-Martin et al., PLoS ONE 8, e69523 (2013)].
- We have identified the protein phosphatase PP1 regulatory subunit R6 (PPP1R3D) as a new substrate of the laforin-malin complex. This complex ubiquitinates R6 by attaching K63-linked ubiquitin moieties leading to a reduction in its glycogenic activity [Rubio-Villena et al., Int. J. Biochem. Cell. Biol. 45, 1479-1488 (2013)].
- In laforin deficient cellular models we have detected lower levels of Trx1, what suggests a possible impairment in the oxidative stress conditions in Lafora disease patients [Garcia-Gimenez, et al., Free Rad. Biol. Med. 65, 347-359 (2013)].
- We have observed that the AMPKbeta subunit is sumoylated by the E3-SUMO ligase PIASy. This sumoylation is specific of the AMPKbeta2 isoform, being absent in AMPKbeta1. This modification increases the kinase activity of the AMPK trimeric complex and prevents its ubiquitination by E3-ubiquitin ligases [Rubio et al., Mol Biol Cell. 24, 1801-1811 (2013)].

In addition, I would like to mention the opportunities that were given to present our work in international forums:

- First European workshop on AMPK, Maastricht (The Netherlands). Title: The progressive myoclonus epilepsy of the Lafora type defines novel functions for AMPK".
- International Workshop VLC/CAMPUS on intracellular protein degradation in neurodegenerative diseases, Valencia (Spain). Title: "Lafora disease, more than just a glycogen related disorder".

PROGRAMME:
Mitochondrial Medicine

Group U743

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Main lines of research

- Global Cerebral Hipomyelination. Pathogenic mechanisms of the disease caused by mutations in aralar/AGC1 studied with the use of AGC1 KO mice. Effects on myelination, formation of brain N-acetyl-aspartate, glial glutamate and glutamine synthesis. Possible implication of aralar/AGC1 inl diseases characterized by low levels of brain N-acetylaspartate.
- Charcot-Marie-Tooth disease. Alterations in calcium signaling mechanisms, particularly calcium signaling to mitochondria in forms of CMT caused by mutations in GDAP1 and MFN2.
- Mitochondrial pathology: 1. Possible implication of SCaMCs in mitochondrial diseases characterized by deletions in DNAmit deletions and ophthalmoplegia, 2) Possible implication of mutations in SCaMC-3 in human disease associated with deletions or depletion of liver, but not muscle, DNAmit.
- Regulation of calcium signaling to mitochondria and calcium handling by mitochondria. Role of the calcium uniporter and calcium regulated mitochondrial carriers Aralar/AGC1 and SCaMCs. Role of these carriers in deregulation of mitochondrial calcium. Involvement in human pathology.
- Tissue-specific mechanisms of oxidative phosphorylation regulation.
- Mitochondrial retrograde signaling to nuclei as a possible target in mitochondrial pathologies.

* At the expense of Project

Most relevant scientific articles

- Llorente-Folch I, Sahún I, Contreras L, Casarejos MJ, Grau JM, Saheki T, Mena MA, Satrústegui J, Dierssen M, Pardo B. (2013) AGC1-malate aspartate shuttle activity is critical for dopamine handling in the nigrostriatal pathway. J. Neurochem. 124:347-62.
- Amigo I, Traba J, González-Barroso MM, Rueda CB, Fernández M, Rial E, Sánchez A, Satrústegui J, del Arco A. (2013) Glucagon regulation of oxidative phosphorylation requires an increase in matrix adenine nucleotide content through Ca2+ activation of the mitochondrial ATP-Mg/Pi carrier SCaMC-3. J Biol Chem. 288: 7791-802.
- Llorente-Folch I, Rueda CB, Amigo I, del Arco A, Saheki T, Pardo B, Satrústegui J. (2013) Calcium-regulation of mitochondrial respiration maintains ATP homeostasis and requires ARALAR/AGC1-malate aspartate shuttle in intact cortical neurons. J. Neurosci. 33:13957-71.
- Du J, Cleghorn W, Contreras L, Linton JD, Chan GC, Chertov AO, Saheki T, Govindaraju V, Sadilek M, Satrústegui J, Hurley JB. (2013) Cytosolic reducing power preserves glutamate in retina. Proc. Natl. Acad. Sci. U S A.110:18501-6.
- Pla-Martín D, Rueda CB, Estela A, Sánchez-Piris M, González-Sánchez P, Traba J, de la Fuente S, Scorrano L, Renau-Piqueras J, Alvarez J, Satrústegui J, Palau F. (2013) Silencing of the Charcot-Marie-Tooth disease-associated gene GDAP1 induces abnormal mitochondrial distribution and affects Ca2+ homeostasis by reducing store-operated Ca2+ entry. Neurobiol Dis. 55:140-51.

Highlights

- The Unit has been incorporated as member of the Instituto de Investigación Sanitaria Fundación Jiménez Diaz (July 2014) and obtained a research contract from IIS-FJD.
- We have advanced in the knowledge of the role of the Ca2+-dependent mitochondrial metabolite carriers in mitochondrial Ca2+ signaling and in the regulation of glutamate levels in nervous tissue, and in the role of GDAP1 deficiency in CMT.
- We have found that the ATP-Mg/Pi carrier SCaMC-3/Slc25a23 participates in the hepatic response to glucagon in vivo (Amigo et al., JBC) by transporting adenine nucleotides to the matrix, which was permissive in increasing hepatocyte respiratory capacity.
- We have established the role of Ca2+ as regulator of respiration in intact neurons, independently of the effect of Ca on ATP consumption, and determined the relative role of SCaMC-3 and Aralar/AGC1/Slc25a12 in regulation of respiration and maintenance of cell ATP levels in response to different workloads (Llorente-Folch et al., J. Neurosc.).
- We have developed methods to estimate stimulation of respiratory activity in intact cells, the use of probes (chemical or DNA-encoded) to measure mitochondrial and cytosolic ATP and Ca2+ and cytosolic Na+. These methods have been used to study physiopathological mechanisms in Charcot-Marie-Tooth disease due to mutations in GDAP1 (in collaboration with Palau unit), revealing that GDAP1 deficiency results in an altered mitochondrial distribution and SOCE "Store-Operated Calcium Entry" activity (Pla-Martín et al., Neurobiol Dis).
- In collaboration with James Hurley (Univ. Washington) we have used metabolomics (gas chromatography/mass spectroscopy and 13C labeling) to study the role of Aralar/AGC1/Slc25a12 in intra- and intercellular traffic of amino acids and glutamine synthesis, finding that in retina, Aralar/AGC1-malate aspartate shuttle protects glutamate from oxidation (Du et al., PNAS).

PROGRAMME:
Genetic Medicine

Group U744

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Main lines of research

- Clinical and molecular study of rare genetic epilepsias. Molecular basis of Lafora myoclonic epilepsy.

Most relevant scientific articles

- Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, Crompton DE, Hughes JN, Bellows ST, Klein KM, Callenbach PM, Corbett MA, Gardner AE, Kivity S, Iona X, Regan BM, Weller CM, Crimmins D, O'Brien TJ, Guerrero-López R, Mulley JC, Dubeau F, Licchetta L, Bisulli F, Cossette P, Thomas PQ, Gecz J,Serratosa J, Brouwer OF, Andermann F, Andermann E, van den Maagdenberg AM,Pandolfo M, Berkovic SF, Scheffer IE. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. Nat Genet 2013 May;45(5):546-51. doi: 10.1038/ng.2599. Epub 2013 Mar 31. FI: 35.21.
- Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, Alber M, Geider K, Laube B, Schwake M, Finsterwalder K, Franke A, Schilhabel M, Jähn JA, Muhle H, Boor R, Van Paesschen W, Caraballo R, Fejerman N, Weckhuysen S, De Jonghe P, Larsen J, Møller RS, Hjalgrim H, Addis L, Tang S, Hughes E, Pal DK, Veri K, Vaher U, Talvik T, Dimova P, Guerrero López R, Serratosa JM, Linnankivi T, Lehesjoki A-E, Ruf S, Wolff M, Buerki S, Wohlrab G, Kroell J, Datta AN, Fiedler B, Kurlemann G, Kluger G, Hahn A, Haberland

E, Kutzer C, Sperner J, Becker F, Weber YG, Feucht M, Steinböck H, Neophythou B, Ronen GM, Gruber-Sedlmayr U, Geldner J, Harvey RJ, Hoffmann P, Herms S, Altmüller J, Toliat M, Thiele H, Nürnberg P, Wilhelm C, Stephani U, Helbig I, Lerche H, Zimprich F, Neubauer BA, Biskup S, von Spiczak S. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. Nature Genetics 2013 Sep;45(9):1067-72. FI: 35.21.

- Suls A, Jaehn JA, Kecskés A, Weber Y, Weckhuysen S, Craiu DC, Siekierska A,Djémié T, Afrikanova T, Gormley P, von Spiczak S, Kluger G, Iliescu CM, Talvik T,Talvik I, Meral C, Caglayan HS, Giraldez BG, Serratosa J, Lemke JR,Hoffman-Zacharska D, Szczepanik E, Barisic N, Komarek V, Hjalgrim H, Møller RS,Linnankivi T, Dimova P, Striano P, Zara F, Marini C, Guerrini R, Depienne C,Baulac S, Kuhlenbäumer G, Crawford AD, Lehesjoki AE, de Witte PA, Palotie A,Lerche H, Esguerra CV, De Jonghe P, Helbig I; EuroEPINOMICS RES Consortium. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. Am J Hum Genet 2013 Nov 7;93(5):967-75. FI: 11.680.
- Gómez-Tortosa E, Gallego J, Guerrero-López R, Marcos A, Gil-Neciga E, Sainz MJ, Díaz A, Franco-Macías E, Trujillo-Tiebas MJ, Ayuso C, Pérez-Pérez J. C9ORF72 hexanucleotide expansions of 20-22 repeats are associated with frontotemporal deterioration. Neurology. 2013 Jan 22;80(4):366-70. FI: 8.25.
- García-Cabrero AM, Guerrero-López R, Giráldez BG, Llorens-Martín M, Avila J, Serratosa JM, Sánchez MP. Hyperexcitability and epileptic seizures in a model of frontotemporal dementia. Neurobiol Dis. 2013 Oct;58:200-8. FI: 5.62.

Highlights

Unit 744 of CIBERER aims to identify and characterize genes involved in focal or generalized familial epilepsies and rare forms of epilepsy to generate diagnostic and therapeutic tools that improve the care of patients affected by these diseases. During the year 2013 we have obtained the following results:

We have designed a diagnostic panel for the analysis of genes associated with rare forms of epilepsy and epileptic encephalopathies in childhood to assess its utility as a diagnostic tool and to transfer it to Neurology and Genetics Services of Fundación Jiménez Díaz.

We have continued with the initiative led by U744 (Spanish Group of Genetics of Childhood Epilepsy , GEGEI , www.gegei.es)

At international level, currently we represent Spain in the "Collaborative Research Project (CRP) on Rare Epilepsy Syndromes of EUROEPINOMICS (European Science Foundation).

Collaborative studies on epilepsy, in which unit U744 has been involved, have identified new genes and susceptibility loci in different types of rare epileptic syndromes (see publications section).

We have continued with the study of animal models of Lafora disease and frontotemporal dementia.

Our group is actively involved in clinical trials (Phase II, III and IV) and currently is running an in-house designed clinical trial that includes the development and use of devices to monitor seizures at home.

We have also participated in the official clinical practice guideline on epilepsy of the Spanish Neurological Society.

Our group works closely with the Dementia Unit at the Fundación Jiménez Díaz and has collaborated in studies at European level on Huntington 's disease.

PROJECTS

SAF2010/18586 (2010-2014) and EUI-EURC-2011-4325 (2011-2014) from Ministry of Economy and Competitiveness.

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U745

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Main lines of research

- Genetics and molecular biology of Fanconi Anemia. Genetic characterization of Fanconi patients and identification of new genes involved in the disease and into hereditary breast cancer syndrome and its functions.
- Development of new diagnostic and therapeutic tools on Fanconi anemia, including gene therapy and regenerative medicine.
- Mechanism of genomic instability and predisposition to cancer. Study of DNA lesions repair and biological and clinical consequences of repair mechanisms failure.
- Fanconi/BRCA pathway in cancer. Implication of Fanconi genes in cancer and use of them as a therapeutic target against cancer.

Most relevant scientific articles

- Bogliolo M., Schuster B., Stoepker C., Derkunt B., Su Y., Raams A.,Trujillo JP., Minguillón J., Ramírez MJ., Pujol R., Casado JA., Baños R., Rio P., Knies K., Zúñiga S., Benítez J., Bueren JA., Jaspers N., Schärer O., De Winter J., Detlev Schindler D.* and Surrallés J.*. Mutations in ERCC4, Encoding the DNA-Repair Endonuclease XPF, Cause Fanconi anemia. Am. J. Hum, Genet. 2013 May 2 ; 92, 1-7.
- Aulinas A, Ramírez MJ, Barahona MJ, Mato E, Bell O, Surrallés J, Webb SM. Telomeres and endocrine dysfunction of the adrenal and GH/IGF-1 axes.. Clin Endocrinol. 2013. 79,751-759.
- Osorio A, Bogliolo M, Fernández V, Barroso A, de la Hoya M, Caldés T, Lasa A, Ramón y Cajal T, Santamariña M, Vega A, Quiles F, Lázaro C, Díez O, Fernández D, González-Sarmiento R, Durán M, Piqueras JF, Marín M, Pujol R, Surrallés J, Benítez J. Evaluation of rare variants in the new Fanconi Anemia gene ERCC4 (FANCQ) as familial breast/ ovarian cancer susceptibility alleles. Human Mutation. 2013. Dec;34(12);1615-8.

Highlights

Our main research achievement in 2013 was the identification of a novel Fanconi anemia (FA) gene, FANCQ in collaboration with Javier Benitez (U706) and Juan Bueren (U710) teams. This gene, also known as ERCC4 or XPF, was already involved in two other syndromes, xeroderma pigmentosum and XFE-type progeria. Our main difficulty was to prove and mechanistically explain why different mutations in the same gene cause three clinically non-overlapping DNA damage response syndromes. The study was published in Am J Hum Genetics and it was recognized with two international research awards: Discovery Award 2013 (Fanconi Anemia Research Fund. Houston. USA) and Award of Appreciation 2013 (German Fanconi Anemia Family Support Group. Gersfed. Frankfurt. Germany). In addition, in the frame of an intramural project and in collaboration with Javier Benitez and Jose Fernandez-Piqueras teams (CIBERER Units U706 and U749), we investigated the role of this novel FA gene in familiar breast cancer. With this purpose ERCC4/FANCQ/XPF was sequenced in over 1597 cases and 854 controls and all identified mutations were functionally studied. The results were published in Hum Mut and exclude FANCQ as a novel breast cancer susceptibility gene. However, we found more carriers that expected in the general population suggesting an excess of embryo lethality of biallelic FANCQ mutations.

PROGRAMME:
Inherited Metabolic Medicine

Group U746

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Main lines of research

- Study of new gene and pharmacological therapies for organic acidemias, and congenital disorders of glycosilation.
- Study of mitochondrial dysfunction and oxidative stress in meatabolic hereditary diseases. Antioxidant effect.
- Biochemical, genetic and proteomic analysis of glycosylation congenital disorders.
- Biochemical and genetic study of creatine brain defects.
- Enzyme replacement therapy in inherited metabolic diseases.
- Application of genomic methods to improve the diagnosis of IMD: arrays and next generation sequencing.

Most relevant scientific articles

- Pharmacological chaperones as a potential therapeutic option in methylmalonic aciduria cblB type. Jorge-Finnigan A, Brasil S, Underhaug J, Ruíz-Sala P, Merinero B, Banerjee R, Desviat LR, Ugarte M, Martínez A, Pérez B. Humman Molecular Genetics (2013) 22(18):3680-9.
- A novel regulatory defect in the Branched-Chain Alpha-ketoacid dehydrogenase complex due to a mutation in the PPM1k Gene causes a mild variant phenotype of maple Syrup Urine disease. Oyarzabal A, Martínez-Pardo M, Merinero B, Navarrete R Desviat LR, Ugarte M, Rodríguez-Pombo P. Human Mutation (2013) 34(2): 355-362.
- Clinical Biochemical and molecular studies in pyridoxine-dependent epilepsy. antisense therapy as possible new therapeutic option. Belén Pérez, Luis González Gutiérrez-Solana, Alfonso Verdú, Begoña Merinero, Patricia Yuste-Checa, Pedro Ruiz-Sala, Rocio Calvo, Anil Jalan, Laura López Marín, Oscar Campos, Maria Ángeles Ruiz, Marta San Miguel, Maria Vázquez, Margarita Castro, Isaac Ferrer, Rosa Navarrete, Lourdes Ruiz Desviat, Pablo Lapunzina, Magdalena Ugarte and Celia Pérez-Cerdá. Epilepsia (2013) 54(2) 239-248.
- A novel congenital disorder of glycosylation type without central nervous system involvement caused by mutations in the phosphoglucomutase 1 gene. Pérez B, Medrano C, Ecay MJ, Ruiz-Sala P, Martínez-Pardo M, Ugarte M, Pérez-Cerdá C. J Inherit Metab Dis. (2013) 36(3):535-42.
- Functional characterization of novel genotypes and cellular oxidative stress studies in propionic acidemia. Gallego-Villar L, Pérez-Cerdá C, Pérez B, Abia D, Ugarte M, Richard E, Desviat LR. J Inherit Metab Dis. (2013) 36(5):731-40.

Highlights

Our work is focused on the biochemical and genetic diagnosis of inherited metabolic diseases and also in the research of their molecular basis. In the last year we have expanded the metabolomics (quantification of vitamins, sugars and mucopolysaccharides) and enzymatic (CBS and LCHAD) analysis to detect of a number of new metabolic disorders such as vitamin disorders, glycogen storage and galactosemia disorders and lysosomal disorders.

We have generated a proof-of-concept to use the next generation sequencing in the clinical practice to perform the differential diagnosis of hyperphenylalaninemias. Additionally we have defined the mutational spectrum of piridoxine-dependent epilepsy in our country and we have identified for first time mutations in the PPM1K gene encoded for the phosphatase which regulates the BCKDH complex. Finally we have identified mutations in the PGM1 gene in a patient with congenital disorder of glycosylation (CDG) connecting the CDG with the glycogenosis storage disorders.

Regarding the research in new therapies we have extensively analysed the effect of mutants on the splicing and folding processes of genes and protein respectively, describing several new molecular targets for therapeutic intervention, in the field of what is known as personalized genetic medicine.

The group has developed a gene specific antisense RNA-based therapy for splicing defects in a number of IMD. We are also working on the secondary mitochondrial dysfunction present in organic acidurias defects and we have postulated that ROS could be a phenotypic modifier in these disorders and also a new therapeutic target to treat with antioxidants. We have reported the proof-of concept for application of pharmacological chaperones in the treatment of methylmalonica aciduria cblB type.

A high-throughput screening from a large drug library has been applied and several hits have identified, one of them patented, which in combination with B12 are able to improve the stability and activity the mitochondrial protein adenosylcobalamin transferase in a therapeutic range. Also we have demonstrated that is able to reach tissue-disease organs such as brain and liver.

PROGRAMME:
Endocrine Medicine

Group U747

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Main lines of research

- Morbidity and mortality, low grade inflammation and cardiovascular disease risk of patients suffering from acromegaly and Cushing's syndrome.
- Neuroradiological, neuropsychiatric and hormonal correlation in patients with endogenous hypercortisolism.
- Spanish Acromegaly Registry.
- Neuromyopathy due to adult GH deficiency as a model of muscle atrophy.
- Etiology of cardiopathy in acromegaly and its relation to body composition.
- ERCUSYN: European Registry on Cushing's Syndrome. Maintenance and exploitation of this database which contains data on over 900 patients and is the largest one ever on patients with this diagnosis.
- Role of telomeres in endocrine diseases. In collaboracton with the group of J Surrallés U745.

Most relevant scientific articles

- X Badia; M Roset; E Valassi; H Franz; A Forsythe; S M Webb. Mapping CushingQOL scores to EQ-5D utility values using data from the European Registry on Cushing's syndrome (ERCUSYN). Quality of Life Research 2013; 22 (10):2941-50: FI 2.421. 1º cuartil (18 /82 HEALTH CARE SCIENCES & SERVICES). ISSN: 1573-2649.
- MJ Barahona; E Resmini; D Viladés; G Pons Lladó; R Leta; T Puig; SM Webb. Coronary artery disease detected by multislice computed tomography in patients after long-term cure of Cushing's syndrome. THE JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM 201; 98(3):1093 – 1102. FI 6.430, 1º cuartil ENDOCRINOLOGY & METABOLISM (13 / 122). ISSN: 0021-972X 1945-7197.
- Resmini E, Santos A, Gómez-Anson B, López-Mourelo O, Pires P, Vives Y, Crespo I, Portella MJ, de Juan-Delago M, Webb SM. Functional abnormalities in the hippocampus of patients with cured Cushing's syndrome, detected by brain spectroscopy. CLINICAL ENDOCRINOLOGY. 79(5): 700-707; 2013. FI 3.396; 46/121 – 2º cuartil- ENDOCRINOLOGY & METABOLISM. ISSN 1365-2265.
- Aulinas, A ; Ramirez, MJ; Barahona, MJ; Mato, E ; Bell, O ; Surralles, J; Webb, SM. Telomeres and endocrine dysfunction of the adrenal and GH/IGF-1 axes. CLINICAL ENDOCRINOLOGY. 79(6): 751-759; 2013. FI 3.396; 46/121 – 2º cuartil- ENDOCRINOLOGY & METABOLISM. ISSN 0300-0664.
- Webb, SM. How good is perceived health-related quality of life in patients treated for non-functioning pituitary adenomas? CLINICAL ENDOCRINOLOGY 78 (1): 21-22; 2013. FI 3.396; 46/121 – 2º cuartil- ENDOCRINOLOGY & METABOLISM. ISSN 0300-0664.

Highlights

U747 is a clinical group devoted to patient-oriented research on pituitary diseases, with a translational component to the NHS, responsible for RD registries and collaborates with patient associations. In translational activities the PI is a member of EUCERD, EPIRARE, Orphanet-España and coordinator of the investigation Program Endocrine Medicine within CIBERER. Since 1982 she runs the Pituitary Clinic.

All publications are on endocrine RD and 3 in 2013 are in collaboration with other CIBERER groups (U725A y U745).

The communication submitted by the CIBERER-hired Postdoc E Resmini to the European Congress Endocrinology (Copenhaguen 2013) was selected as of general interest, greatly echoed in international media (including CIBERER press notes), and published in Clinical Endocrinology.

In 2013 the 2nd year of the competitive public project (ISCIII, PI 11-0001) and another private competitive one of the Fundación Merck-Serono have been developed and a postdoctoral Juan de la Cierva grant was obtained (E Valassi).

In transfer activity to the productive sector we conducted clinical trials (phases 2, 3 and 4), continued epidemiological studies and offered advice on pituitary RD, with which income the research nurse O Roig continues to be hired (initially by CIBERER until 2011). With the funds as author copyright rights of the disease-specific questionnaires for Cushing's syndrome and acromegaly (and recently also for primary hyperparathyroidism) held by the PI and associated researcher X Badia, a predoctoral fellow is hired, who initially came to the group through a "starting grant" of the CIBERER in 2010.

In 2013 an agreement between Novartis and the ESE (European Society Endocrinology) to support the ERCUSYN (European Registry on Cushing's sd) registry materialized; this registry began in 2007 thanks to the EU PHP funding, and currently guarantees its viability for 5 years. U747 is the European coordinator of this registry.

In march 2013 the associated researcher Mª Antonia Martínez Momblán defended her PH D Thesis on Cushing's syndrome.

PROGRAMME:
Genetic Medicine

Group U748

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Main lines of research

- Neural cell models of frataxin deficiency.
- Molecular and cellular physiopathology of Friedreich's ataxia.
- Gene therapy in models of Friedreich's ataxia.
- Biology of stem cells of the olfactory mucosa.
- Application in cell therapy and regenerative medicine.

Highlights

We have performed transcriptomic and proteomic studies (in collaboration with the group of CIBERER U732) of various cellular models of frataxin deficiency that have allowed us to identify some candidates that could serve as biomarkers and therapeutic targets for Friedreich's ataxia.

We have initiated two projects aimed at exploring novel approaches for the therapy of Friedreich ataxia, one focused on the development of gene therapy and another addressing the use of agonists of neurotrophic factor receptors.

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U749

Group Members

STAFF MEMBERS

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ASSOCIATED MEMBERS

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Main lines of research

- Genetic and epigenetic alterations in T-lymphoblastic lymphomas.

Most relevant scientific articles

- Elena González-Gugel, María Villa-Morales, Javier Santos, María J. Bueno, Marcos Malumbres, Socorro María Rodríguez-Pinilla, Miguel Ángel Piris and José Fernández-Piqueras. Down-regulation of specific miRNAs enhances the expression of the gene Smoothened and contributes to T-cell lymphoblastic lymphoma development. Carcinogenesis (2013) 34 (4): 902-908. doi: 10.1093/carcin/bgs404. Epub 2013 Jan 3. PMID: 23288923.
- Almoguera, B., Riveiro-Alvarez,R., López-Castroman, J., Dorado, P., Vaquero-Lorenzo, C., Fernández-Piqueras, J., LLerena, A., Abad-Santos, F., Baca-García, E., Dal-Ré, R., Ayuso C., & Spanish Consortium of Pharmacogenetics Research in Schizophrenia. (2013). Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. Pharmacogenomics J.13 (2): 197-204. doi: 10.1038/tpj.2011.57. PMID: 22212732.

- Berta Almoguera, Rosa Riveiro-Alvarez, Jorge López-Castroman, Pedro Dorado, Concepción Vaquero-Lorenzo, José Fernández-Piqueras, Adrián LLerena, Francisco Abad-Santos, Enrique Baca-García, Rafael Dal-Ré, Carmen Ayuso Spanish Consortium of Pharmacogenetics Research in Schizophrenia. CYP2D6 poor metabolizer status might be associated with better response to risperidone treatment. Pharmacogenetic Genomics (2013) 23 (11): 627-30. PMID: 24026091.
- Ana Osorio, Massimo Bogliolo, Victoria Fernández, Alicia Barroso, Miguel de la Hoya, Trinidad Caldés, Adriana Lasa, Teresa Ramón y Caja, Marta Santamariña, Ana Vega, Francisco Quiles, Conxi Lázaro, Orland Díez, Daniel Fernández, Rogelio González-Sarmiento, Mercedes Durán, José Fernández Piqueras, María Marín, Roser Pujol, Jordi Surrallés, Javier Benítez. Evaluation of rare variants in the new Fanconi Anemia gene ERCC4 (FANCQ) as familial breast/ovarian cancer susceptibility alleles. Human Mut (2013) 34: 1615-1618.

Highlights

MOST REMARKABLE RESULTS:

- We demonstrated that the activation of the Hedgehog signalling pathway is crucial to T-cell lymphoblastic lymphoma (T-LBL) development, and that this occur due to over-expression of SMO by down-regulation of several microRNAs. So, adjuvant treatment with cyclopamine would be a good choice.
- The identification of gene variants associated with response to risperidone treatment (in collaboration with Dra. C. Ayuso, CIBERER).
- And the evaluation of rare variants in the Fanconi Anemia gene ERCC4 as familial breast/ovarian cancer susceptibility alleles (in collaboration with the team of Jordi Surralles y Javier Benítez at CIBERER).

PROJECTS AWARDED IN 2013:

2.1-Actión COST (EC-BM0901) (2013).

2.2- S2010/BMD-2470 (OncoCycle-CM) (renewed for the 2013-2015 period year).

2.3-ACCI-CIBERER-12-03, ISCIII. (2013-2014)

2.4- IIS-FJD (specific action for one year 2013-14)

TRANSLATING ACTIVITIES

- Integration in the Institute for Health Research, FJD" (IIS-FJD).
- Production of Genetic and Epigenetic reports about T-LBL patients for the "Haematological Service of the HU FJD", and discussion about clinical cases collaboratively studied.
- Staff member of the "Committee of Experts on Human Genetics on the Madrid Autonomous Community, and participation in a session.
- President (Chairman) of the Scientific Committee of FARPE-FUNDALUCE, and participation in a meeting.

OTHER ACTIVITIES

- Seven presentations in national and international conferences.
- Teaching classes in multiple masters: Masters in Molecular Oncology (CNIO), Genetics and Cellular Biology (UAM), en Molecular Biomedicine (subjects "Immune and inflammatory diseases" and "Molecular Oncology") and "University Expert in Clinical Genetics" course (UA).
- Supervision of three " Final Degree Projects".
- Coordinator and speaker of the "Training Course for Professors" at CBMSO .
- Teaching of "The Science of the future" (University programme for mature students).
- Speacker in long working hours on "Health and Fight against doping in Sport" (INEF).
- Coordinator for Biomedicine in the Spanish Evaluation Agency (ANEP, MINECO)

PROGRAMME:
Inherited Metabolic Medicine

Group U750

Group Members

STAFF MEMBERS
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Main lines of research

- Neurogenetics.
- Myelin.
- Neurodegeneration.
- Ion channels.
- Glial regulation.
- Myotonia.
- Bartter síndrome.

Most relevant scientific articles

- Hoegg-Beiler MB, Sirisi S, Orozco IJ, Ferrer I, Hohensee S, Auberson M, Gödde K, Vilches C, López de Heredia M, Nunes V*, Estévez R*, Jenstch TJ*. Disrupting MLC1 and GlialCAM and ClC-2 interactions in leukodystrophy entails glial chloride channel dysfunction Nature communications DOI:10.1038/ncomms4475 (2014).
- Capdevila-Nortes X, López-Hernández T, Apaja PM, López de Heredia M, Sirisi S. Callejo G, Arnedo T, Nunes V, Lukacs GL, Gasull X, Estévez R. Insights into MLC pathogenesis: GlialCAM is an MLC1 chaperone required for proper activation of volume-regulated anion currents. Hum Mol Gen 22: 4405-16 (2013).
- van der Knaap MS, Boor I, Estévez R. Megalencephalic leukoencephalopathy with subcortical cysts: chronic white matter oedema due to a defect in brain ion and water homeostasis. Lancet Neurol 11: 973-85 (2012).
- Jeworutzki E, López-Hernández T, Capdevila-Nortes X, Sirisi S, Bengtsson L, Montolio M, Zifarelli G, Arnedo T, Müller CS, Schulte U, Nunes V, Martínez A, Jentsch TJ, Gasull X, Pusch M, Estévez R. GlialCAM, a protein defective in a leukodystrophy, serves as a ClC-2 Cl(-) channel auxiliary subunit. Neuron 73: 951-61 (2012). Comment in Neuron (2012), 73.
- López-Hernández T, Ridder MC, Montolio M, Capdevila-Nortez X, Polder E, Sirisi S, Duarri A, Schulte U, Fakler B, Nunes V, Scheper GC, Martínez A, Estévez R*, van der Knaap MS*. GlialCAM mutations cause megalencephalic leukoencephalopathy with subcortical cysts, and also benign familial macrocephaly and macrocephaly with retardation and autism. Am J Hum Genetics, 88:422-32 (2011) Comment in Am J Hum Gen (2011).

Highlights

In this year 2013 our group has made progress in the understanding of the molecular basis of the rare disease megalencephalic leukoencephalopathy (Known as MLC). Previous of our group have identified the second disease gene, which is called GLIALCAM. During this year, we have been able to understand the biochemical relationship between the two proteins involved in the disease. We have also generated and studied KO animal models in mice and zebrafish. The studies of these models have allowed clarifying the fact that MLC patients with mutations in MLC1 or GLIALCAM share the same clinical symptoms. These models could be used in a near future to develop new therapies for patients with MLC.

During 2013, our group obtained funding from European Leukodystrophy Association (ELA) for the project MLC disease: indentification of proteins which could modulate the disease phenotype, from Ministerio de Economía y competitividad (MCOC) for the project Subunidades reguladoras de canales de CI-CLC y sus enfermedades asociadas Leucoencefalopatía megalencefálica y síndrome de Bartter, and from AFM (Assocation Française contre les myopathies) for the project Development and characterization of a zebrafish model of myotonia congénita. In general, our group is studying rare genetic diseases caused by defects in chloride channels.

PROGRAMME:
Genetic Medicine

Group U751

Group Members

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Main lines of research

- Physiopathology of the glutamatergic and glycinergic pathways in the central nervous system in mammals.
- Study of glycine-mediated neurotransmission in the brain stem and spinal cord. Neuromuscular system disorders relating to the glycinergic system: hyperekplexia.
- Molecular basis for glutamatergic neurotransmission involved in memory and learning processes and in pathological processes.

Most relevant scientific articles

- Arribas-González E, Alonso-Torres P, Aragón C, López-Corcuera B. Calnexin-assisted biogenesis of the neuronal glycine transporter 2 (GlyT2). PLoS One 2013; 8(5):e63230 PubMed.
- de Juan-Sanz J, Núñez E, López-Corcuera B, Aragón C. Constitutive endocytosis and turnover of the neuronal glycine transporter GlyT2 is dependent on ubiquitination of a C-terminal lysine cluster. PLoS One 2013; 8(3):e58863 PubMed.
- de Juan-Sanz J, Núñez E, Villarejo-López L, Pérez-Hernández D, Rodríguez-Fraticelli AE, López-Corcuera B, Vázquez J, Aragón C. Na+/K+-ATPase Is a New Interacting Partner for the Neuronal Glycine Transporter GlyT2 That Downregulates Its Expression In Vitro and In Vivo. J Neurosci 2013; 2013 Aug 28. 33(35):14269-81 PubMed.
- B. Cubelos, C. Gimenez and F. Zafra. Localization of the glycine transporter GLYT1 in glutamatergic synaptic vesicles. Neurochem. Int. 2013 Sep 11. pii: S0197-0186(13)00228-3. doi: 10.1016/j.neuint.2013.09.002. [Epub ahead of print] PMID:24036061.
- Rodríguez, A. Ortega, L.C. Berumen, M.G. García-Alcocer, C. Giménez and F. Zafra. Expression of the System N transporter (SNAT5/SN2) during development indicates its plausible role in glutamatergic neurotransmission. Neurochem. Int. 2013 Dec 11. pii: S0197-0186(13)00308-2. doi: 10.1016/j.neuint.2013.11.011. [Epub ahead of print] PMID:24333324.

Highlights

Throughout the year 2013 the group develops two MINECO Research Projects (Pathophysiology of glycine transporters in glycinergic neurotransmission: hyperekplexia and pain SAF2011 - 28674 PI: Beatriz López Corcuera 2012-2014; Glutamatergic hypothesis of schizophrenia.: Molecular mechanisms of transport of glutamate and glycine at glutamatergic synapses SAF2011 - 29961 PI: Zafra Francisco Gómez 2012-2014) both directly related to the objectives and lines of rare diseases. We have concluded a four-year project funded by the Community of Madrid, and coordinated by Cecilio Giménez) .

Two years ago we started with the U753 group led by Dr Paul Lapunzina and the Association of Patients with Dravet a genetic screening program and study of Dravet patients by biochemical , electrophysiological and molecular and cell biology techniques. So far more than 450 mutations have been found in a cohort of Spanish and non-Spanish patients, that we have grouped by topological location in the protein, and 12 of them are being studying in detail. The results are advanced, are very interesting and innovative and will publish shortly.

Results published in 2013 are related to the regulation of the neuronal glycine transporter GlyT2 a protein which is susceptible to mutations responsible for hyperekplexia (in 2012 we described a new mutation causing hyperekplexia) a rare disease. Until now, we have detected 80 cases of hiperekplexia with the Group U753 and two UK groups (Drs. Harvey and Rees) . Other publications appear in 2013 are related with glutamatergic neurotransmission and schizophrenia.

PROGRAMME:
Inherited Metabolic Medicine

Group U752

Group Members

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Roca Espiau, Mercedes
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Main lines of research

- Gaucher disease epidemiology, in Spain: National Registry acredited by ISO 9001 (Num EC2751/07).
- Genetic analysis and search of genes related to clinical heterogeneity. Directed mutagenesis. DNA, serum, plasma and leukocyte patient samples biobank.
- Study of biomarkers and inflammatory cytokines and its relationship with response to treatment.
- Study of bone disease by imaging techniques and its relationship with plasma biomarkers.
- Neurological disease evaluation by clinical, neurophysiological and imaging methods.
- Clinical research of new drugs on clinical trials (OGT-011, TKT034, TKT039, Protalix). Independent clinical trial.
- Epidemiology of hematological neoplasias. Gene expression marker study and search of polymorphisms accounting for familial aggregations.
- Approach to study of internalization of nanoparticles containing small drug molecules on monocytes and macrophages and application to treat deposit diseases.
- Analysis of the effect of pharmacological chaperones on protein mutants in Gaucher Disease.
- Plasma miRNAs profile in Haematological malignancies and predictor use to developed acute leukaemia.

Most relevant scientific articles

- Alfonso P, Navascués J, Navarro S, Medina P, Bolado-Carrancio A, Andreu V, Irún P, Rodríguez-Rey JC, Pocoví M, España F, Giraldo P. Characterization of variants in the glucosylceramide synthase gene and their association with type 1 Gaucher disease severity. Hum Mutat.2013;34:1396-403.
- Mateos MV, Hernández MT, Giraldo P et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med. 2013;369: 438-47.
- Alfonso P, Andreu V, Pino-Angeles A, Moya-García AA, García-Moreno MI, Rodríguez-Rey JC, Sánchez-Jiménez F, Pocoví M, Ortiz Mellet C, García Fernández JM, Giraldo P. Bicyclic derivatives of L-idonojirimycin as pharmacological chaperones for neuronopathic forms of Gaucher disease. Chembiochem. 2013;14: 943-9.
- Ben Turkia H, González DE, Barton NW, Zimran A, Kabra M, Lukina EA, Giraldo P et al. Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease. Am J Hematol. 2013; 88:179-84.
- Irun P, Mallén M, Dominguez C, Rodríguez-Sureda V, Alvarez-Sala LA, Arslan N, Bermejo N, Guerrero C, Perez de Soto I, Villalón L, Giraldo P, Pocovi M. Identification of seven novel SMPD1 mutations causing Niemann-Pick disease types A and B. Clin Genet. 2013;84:356-61.

Highlights

PROJECTS FUNDED IN COMPETITIVE CALLS: 1.-FIS PS12/01219. 2.-Etnographic study WP7 of EUCERD Joint Action. 3.-Spanish IRDiRC project IISCIII. 4.-Strategic Action in Health Rio Hortega. 2013. Marcio Andrade Campos CM13/00330.

PROJECTS FUNDED BY COMPANIES: 1.-IIR-ESP-000140 (2013-2014). 2.-L-GENZ-E 003 (2011-2013). 3.-IS12/0004 (2012-2013). 4.-SEGAVELA-VEL-2011-01 (2012-2014). 5.-FAVIO (2011-2013). 6.-Assesment of bone disease and Gaucher disease (2011-2014). 7.-Mutations & polimorphism in NPC1 & NPC2 genes (2011-2013). 8.-Analysis of intestinal sacharidases profile (2012-2014).

CLINICAL TRIALS: 1.-AT1001-011(2011-2013). 2.-PB-06-007 (2008-2013). 3.-CAM-N107A2303 (2008-2013). 4.-GZGD02607 (2008-2014). 5.-CINC424A2401 (2011-2014). 6.-PB-102-F01 (2013-2015).

PATENTS: 1.-61/638.837 (PE-04581). 2.-P201230804.

PRESENTATIONS IN MEETINGS AND FULL CONFERENCES 2013:

4 at Lysosomal Disease Network. 9th Annual WORLD Symposium. Orlando.

An oral at VI REUNION ANUAL CIBERER El Escorial.

2 at XXVII Congreso Nacional de la AEGH. Madrid.

3 at18th Congress de la EHA. Stockholm, Sweden.

8 and a conference at 12th ICIEM. Barcelona.

2 conferences at Symposium: Gaucher Disease in Foco. Coimbra, Portugal.

3 at LV Reunión Nacional de la SEHH y XXIX Congreso Nacional de la SETH. Sevilla.

2 at ASH Annual Meeting and Exposition. New Orleans, USA.

CLINICAL GUIDELINES:

- National guidelines for the management of patients with chronic lymphocytic leukemia. Med Clin; 2013 .141:175.e1-8
- Spanish Guidelines in Gaucher Disease. http://www.ciberer.es

CONTINUED EDUCATION 2013:

DOCTORAL THESIS: Functional study of the GLA gene variants. Javier Gervas Arruga. 11/01/2013. Suitable cum laude. Dir: Pilar Giraldo Castellano, Miguel Pocoví Mieras

- Course Rare Metabolic Diseases. Universidad de Zaragoza.
- Master Rare Diseases. Modulo rare hematological disorders. Universidad Pablo Olavide. Sevilla.
- 17 y 18 Update in Lysosomal disorders for foreing doctors Hospital Universitario Miguel Servet. Zaragoza. Mayo y Septiembre. Zaragoza.
- Advancing knowledge of Gaucher Disease. Mexico DF.
- First Latin America Symposium: "Gaucher Disease Today" Santiago, Chile.
- "Second Course of Medical Education: Gaucher disease, diagnosis and current treatments", Asunción del Paraguay.
- 1st Meeting of Fellows in Gaucher Disease. Santa Marta. Mexico.

PROGRAMME:
Pediatric and Developmental Medicine

Group U753

Group Members

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Belinchón Martínez, Alberta
Campos Barros, Ángel
de Torres Pérez Hidalgo, María Luisa
Del Pozo Maté, Ángela
Delicado Navarro, Alicia
Ezquieta Zubicaray, Begoña
Fernández García-Moya, Luis
García García, Marta
García Miñaur, Sixto
García Santiago, Fé Amalia
Heath, Karen Elise
Magano Casero, Luis F.
Mansilla Aparicio, Elena
Martínez Fernández, Pilar
Martínez Montero, Paloma
Molano Mateos, Jesús
Mori Álvarez, María Ángeles
Nevado Blanco, Julián
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Main lines of research

- Congenital alterations of purine metabolism.
- Subtelomeric rearrangements in patients with idiopathic mental retardation.
- Genetic and functional analysis of genes SHOX and SHOX2 in human growth.
- Overgrowth syndromes. Epidemiology. Clinical presentations and molecular analysis.
- Genetic factors in harmonic hypo.
- Determinants and genetic modifiers of monogenic diabetes.
- Genetic analysis of the ghrelin axis in childhood obesity.
- Study of the physiopathology of neurological manifestations in HPRT deficiency. Implication of purines as neuromodulators.
- Design and optimization of a SNPs microarray for the evaluation of the therapeutic response and toxicity of a series of HIV patients.
- Rearrangements and complex genetic anomalies detected by a CGH array in patients with birth defects, mental retardation or tumors.
- Molecular genetics of hypertrophic myocardiopathy.
- Functional characterization of CLCN1 mutations causing congenital myotonia.
- Molecular study of endothelial dysfunction in human cell models for diabetes and aging.
- Molecular characterization of the 22q11.2 region by MLPA techniques and its correlation with microsatellite genotyping and FISH.
- Pharmacogenetics and pharmacogenomics.
- Autosomal recessive osteogenesis imperfecta.
- Genomic diagnostic tools. Oligo-based microarrays, BCAs and SNPs.
- Genomic, epigenetic and transcriptional study of tumours in polymalformative genetic syndromes.
- Macrocephaly-Capillary Malformation.
- Next Generation Sequencing as a new diagnostic tool in genetic síndromes.
- Dravet Syndrome.

Most relevant scientific articles

- Verdin H, D'haene B, Beysen D, Novikova Y, Menten B, Sante T, Lapunzina P, Nevado J, Carvalho CM, Lupski JR, De Baere E. Microhomology-mediated mechanisms underlie non-recurrent disease-causing microdeletions of the FOXL2 gene or its regulatory domain. PLoS Genet. 2013;9(3):e1003358. doi: 10.1371/journal.pgen.1003358. Epub 2013 Mar 14. PubMed PMID: 23516377; PubMed Central PMCID: PMC3597517.
- Keupp K, Beleggia F, Kayserili H, Barnes AM, Steiner M, Semler O, Fischer B, Yigit G, Janda CY, Becker J, Breer S, Altunoglu U, Grünhagen J, Krawitz P, Hecht J, Schinke T, Makareeva E, Lausch E, Cankaya T, Caparrós-Martín JA, Lapunzina P, Temtamy S, Aglan M, Zabel B, Eysel P, Koerber F, Leikin S, García KC, Netzer C, Schönau E, Ruiz-Perez VL, Mundlos S, Amling M, Kornak U, Marini J, Wollnik B. Mutations in WNT1 cause different forms of bone fragility. Am J Hum Genet. 2013 Apr 4;92(4):565-74. doi: 10.1016/j.ajhg.2013.02.010. Epub 2013 Mar 14. PubMed PMID: 23499309; PubMed Central PMCID: PMC3617378.
- Court F, Martín-Trujillo A, Romanelli V, Garin I, Iglesias-Platas I, Salafsky I, Guitart M, Perez de Nanclares G, Lapunzina P, Monk D. Genome-wide allelic methylation analysis reveals disease-specific susceptibility to multiple methylation defects in imprinting syndromes. Hum Mutat. 2013 Apr;34(4):595-602. doi: 10.1002/humu.22276. Epub 2013 Feb 19. PubMed PMID: 23335487.
- Caparrós-Martín JA, Valencia M, Reytor E, Pacheco M, Fernández M, Perez-Aytes A, Gean E, Lapunzina P, Peters H, Goodship JA, Ruiz-Perez VL. The ciliary Evc/Evc2 complex interacts with Smo and controls Hedgehog pathway activity in chondrocytes by regulating Sufu/Gli3 dissociation and Gli3 trafficking in primary cilia. Hum Mol Genet. 2013 Jan 1;22(1):124-39. doi: 10.1093/hmg/dds409. Epub 2012 Oct 1. PubMed PMID: 23026747.
- Vallespín E, Palomares Bralo M, Mori MÁ, Martín R, García-Miñaúr S, Fernández L, de Torres ML, García-Santiago F, Mansilla E, Santos F, M-Montaño VE, Crespo MC, Martín S, Martínez-Glez V, Delicado A, Lapunzina P, Nevado J. Customized high resolution CGH-array for clinical diagnosis reveals additional genomic imbalances in previous well-defined pathological samples. Am J Med Genet A. 2013 Aug;161A(8):1950-60. doi: 10.1002/ajmg.a.35960.

Highlights

From 2011 to 2013 we have contributed with 97 publications (Mean Impact Factor: 4.5). We can highlight articles in journals like Nat Genet, contributions in Am J Hum Genet as first authors and senior and Plos Genetics, J Med Genet, Plos One, Brain, J Biol Chem, Hum Genet, Hum Mut, Hum Mol Genet etc. We have described a new disease (deletion 8q21), we found 3 new genes (OSX, BMP1 and PLOD2 associated with osteogenesis imperfecta) in collaboration with U760.

From the point of view of technological milestones we have developed genomic technologies, both arrays and NGS platforms, in a structure and unparalleled service in the Spanish hospitals. We have also created the first section of Bionformatics located in a hospital in Madrid, where we hired 3 bioinformatics.

INGEMM has developed, designed and recorded 7 new products with European and U.S. registered mark and managed to market and distribute 2 of them.

We achieved 20 competitive research projects, mainly from public agencies (Ministries/FIS) and some Europeans and Americans, and participated in 2 clinical studies (one national and one international) on RD. We have requested through CIBERER 7 research projects and to date achieved 3 while we requested 2 projects ACCI and got 1.

We have initiated new interdisciplinary clinics, increased the supply of the services portfolio and increased our participation in cooperation and outreach with patients.

INGEMM has 11 sections and has a large number of patients and samples from patients with rare genetic diseases. We are a group of biomedical research to patient, with high translational component. We can develop own research of molecular and/or biological lines and contribute to all groups CIBER providing clinical, cytogenetic and molecular genetic diseases experience.

PROGRAMME:
Genetic Medicine

Group U754

Group Members

STAFF MEMBERS
López Lera, Alberto

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Garrido Herrero, Sofia
Mena de la Cruz, Rocío
Nozal Aranda, Pilar
Sánchez-Corral Gómez, Pilar

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Main lines of research

- The complement system: diagnosis and characterization of pathologies associated with congenital deficiencies of the system and/or their regulation.
- Complement system disorders in renal pathology.
- Identification of modifying genes in clinical manifestations in patients with hereditary angioedema by means of gene expression studies with microarrays.

Most relevant scientific articles

- Hereditary angioedema caused by the p.Thr309Lys mutation in the F12 gene: a multifactorial disease. Gómez-Traseira C, López-Lera A, Drouet C, López-Trascasa M, Pérez-Fernández E, Favier B, Prior N, Caballero T. J Allergy Clin Immunol. 2013 Oct;132(4):986-9. e1-5. doi: 10.1016/j.jaci.2013.04.032. Epub 2013 Jul 10. No abstract available.
- C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and complement regulation. Tortajada A, Yébenes H, Abarrategui-Garrido C, Anter J, García-Fernández JM, Martínez-Barricarte R, Alba-Domínguez M, Malik TH, Bedoya R, Cabrera Pérez R, López Trascasa M, Pickering MC, Harris CL, Sánchez-Corral P, Llorca O, Rodríguez de Córdoba S. J Clin Invest. 2013 Jun 3;123(6):2434-46.
- Disease-modifying factors in hereditary angioedema: an RNA expression-based screening. López-Lera A, Cabo FS, Garrido S, Dopazo A, López-Trascasa M. Orphanet J Rare Dis. 2013 May 20;8:77. doi: 10.1186/1750-1172-8-77.
- An engineered construct combining complement regulatory and surface-recognition domains represents a minimal-size functional factor H. Hebecker M, Alba-Domínguez M, Roumenina LT, Reuter S, Hyvärinen S, Dragon-Durey MA, Jokiranta TS, Sánchez-Corral P, Józsi M. J Immunol. 2013 Jul 15;191(2):912-21. doi: 10.4049/jimmunol.1300269. Epub 2013 Jun 14.
- Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. Bresin E, Rurali E, Caprioli J, Sanchez-Corral P, Fremeaux-Bacchi V, Rodríguez de Cordoba S, Pinto S, Goodship TH, Alberti M, Ribes D, Valoti E, Remuzzi G, Noris M; European Working Party on Complement Genetics in Renal Diseases. J Am Soc Nephrol. 2013 Feb;24(3):475-86. doi: 10.1681/ASN.2012090884. Epub 2013 Feb 21.

Highlights

In 2013 our group initiated new public (Ministerio de Economía y Competitividad) and private (Fundación SENEFRO) research projects. We also received funding from the Centre for Biomedical Network Research on Rare Diseases (CIBERER) in the form of a grant for young researchers (Shuttle grant) for Fernando Corvillo, who obtained his Master degree in Immunology Research on September 2013.

The group started its participation in a paediatric clinical trial on Hereditary Angioedema (HAE) (FIR-086-HGT), and in the post-commercialization registry of Cinryze®, a new drug for HAE. Our participation in the post-commercialization registry of Firazyr (Firazyr-IOS) in the HAE field is ongoing. On the other hand, the group is also contributing to the Collaborative Project "Spanish Rare Disease Registries Research Network (SPAIN-RDR)" within the INTERNATIONAL RARE DISEASE RESEARCH CONSORTIUM (IRDiRC), in order to establish a National Registry for Hereditary Angioedema. The development and validation of a specific HRQoL instrument for HAE (HAE-QoL) has been finished.

During 2013, we set up or optimized several protocols that are important for the detection and characterization of clinically-significant autoantibodies directed against proteins of the complement system (anti-C3, anti-Properdin, anti-Factor B and nephritic factor (C3NEF)). This novel methodology is focused on a translational approach for the study, characterization and diagnosis of complement-related pathologies, as is the case of C3 nephropathies and atypical Haemolytic Uremic Syndrome (aHUS). In this context, we have also started the study of the factor H/FHR protein family in patients of renal pathologies with higher incidence, such as IgA nephropathy.

In 2013 the group's research lines yielded a significant number of peer-reviewed, first-quartile scientific publications, including the five selected in the previous section. We also took part in a workshop hosted by Dr. Rodríguez de Córdoba (U738), with several National and International research groups involved in the study of complement in renal pathologies.

PROGRAMME:
Sensorineural Pathology

Group U755

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Main lines of research

- Usher (USH) syndrome: molecular analysis of the genes involved in Usher syndrome by means of NGS, translation to diagnosis and therapeutic approaches based on gene therapy.
- Experimental models of retinal degeneration: role of oxidative stress and inflammation in neurodegeneration. Pharmacological therapy testing before translational application.
- Translational genomics and identification of biomarkers for the diagnosis of Charcot Marie Tooth neuropathy.
- Identification of prognostic biomarkers for spinal muscular atrophy.
- Search for Huntington's disease modifying genes in a model of the disease in C. elegans.
- Editing the huntingtin gene in patients' cells by means of CRISPR/Cas9.

Most relevant scientific articles

- Sanchez-Jimeno C, Cuadrado-Corrales N, Aller E, García M, Escamez MJ, Illera N, Trujillo-Tiebas MJ, Ayuso C, Millán JM, Del Río M. Recessive Dystrophic Epidermolysis Bullosa: The origin of the c.6527insC mutation in the Spanish population British J Dermatol. 168: 226-229 (2013).
- Aparisi MJ, García-García G, Aller E, Sequedo MD, Martínez-Fernández de la Cámara C, Rodrigo R, Armengot M, Cortijo J, Milara J, Díaz-LLopis M, Jaijo T, Millán JM. Study of USH1 splicing variants through minigenes and transcript analysis from nasal epithelial cells. Plos One. 8: e57506 (2013).
- Ayuso C, Millán JM*, Mancheño M, Dal-Ré R. Informed consent for whole genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. Eur J Hum Genet 21: 1054-1059 (2013).
- Martínez-Fernández de la Cámara C, Sequedo MD, Gómez-Pinedo U, Jaijo T, Aller E, García-Tárraga P, García-Verdugo JM, Millán JM, Rodrigo R. Phosphodiesterase inhibition induces retinal degeneration, oxidative stress and inflammation in cone-enriched cultures of porcine retina. Exp Eye Res. 111: 122-133 (2013).
- Martínez Fernández de la Camara C, Salom D, Sequedo MD, Hervás D, Marín-Lambies C, Aller E, Jaijo T, Díaz-Llopis M, Millán JM, Rodrigo R. Altered antioxidant-oxidant status in the aqueous humor and peripheral blood of patients with retinitis pigmentosa. Plos One. 9: e74223 (2013).

Highlights

RESEARCH:

We have developed a platform for molecular diagnostic of the Usher syndrome, by means of massive parallele sequencing. This platform includes the 11 genes known, to date, to be involved in this disease, and two potential candidate genes. In those patients, with no mutations within the known USH genes, we have sequenced the whole exome to find new genes related to the disease.

We have set up a technique to purify RNA from nasal epithelium, which is known to contain ciliated cells, where USH genes are expressed, to investigate splicing defects in these genes.

We also have developed a protocol to measure the oxidative stress status in aqueous humor and peripheral blood from patients of retinal dystrophies.

We have incorporated to our research group several animal models, such as the rd10 mouse, as a model of retinitis pigmentosa, and the worm C. elegans to study the physiopathology of the Huntington's disease. Moreover, we have developed a fish model of the Usher syndrome, Medaka (Oryzias latipes), by means of knocking-down the Ush2a gene using morpholinos.

SOCIAL WORK:

we collaborate with the Spanish Federation of Rare Diseases (FEDER) in the ENSERIo2 study: "For a health care model for people with rare diseases in the CCAA (Spanish autonomic regions)". We have organized the "second course of Spanish sign language for genetic counseling", and also a meeting on "Research in rare diseases. A social need".

TRAINING:

We have organized the course "Diploma in Molecular Ophthalmology", which is an official subject of the Universitat de València, and the section "Clinical research", of the Program of continuous training in biomedical research for young physicians, of the Hospital La Fe de Valencia.

PROGRAMME:
Sensorineural Pathology

Group U756

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Main lines of research

- Animal models of congenital hypopigmentation diseases: oculocutaneous albinism type I and ocular albinism.
- Animal models of familial Alzheimer's, APP locus mutations.
- ALBINOCHIP: Design and validation of a new system for the genetic diagnosis of all the mutations known associated with any type of albinism.
- New animal model of achromatopsia involved in the cone deficit phenotype observed in the commercial albino mice with no blood relations.
- Optimization of methodologies in animal transgenesis: new methods, protocols and techniques for more efficient generation, analysis and cryopreservation of animal models.
- Pre-clinical therapeutic proposals for albinism, use of L-DOPA and nitisinone in mouse models.
- Mechanism of action of L-DOPA in retinal development in mammals.

Most relevant scientific articles

- Montoliu L (2013) Snowflake, albinism and conservation. Pigment Cell Melanoma Res. 2013 Nov;26(6):786-7. doi: 10.1111/pcmr.12133. Epub 2013 Jul 15.
- Montoliu L, Grønskov K, Wei AH, Martínez-García M, Fernández A, Arveiler B, Morice-Picard F, Riazuddin S, Suzuki T, Ahmed ZM, Rosenberg T, Li W (2014) Increasing the complexity: new genes and new types of albinism. Pigment Cell Melanoma Res. 2014 Jan;27(1):11-8. doi: 10.1111/pcmr.12167. Epub 2013 Oct 17.
- Mártinez-García M, Montoliu L (2013) Albinism in Europe. J Dermatol. 2013 May;40(5):319-24.

Highlights

During 2013, at the U756 of CIBERER, we have continue developing our research projects on albinismo, and with animal models (transgenic and mutante mice) of albinismo, and neurosensorial related pathologies. On the other hand, and in collaboration with U711 (Angel Carracedo) we have continued our activities towards the molecular diagnose of all known mutations associated with albinismo, completing the previous design with new mutations and genes that have appeared recently in the literature. In addition, we have been solving all those cases with patients where only one (or none) of the mutations involved has been characterized, through the use of new approaches involving next generation sequencing strategies. We have also continue expanding our informative and teaching task, through several updates a the web page on albinismo, for people with albinismo and their relatives (http://www.cnb.csic.es/~albino).

Thanks to the 1st European Days of Albinism, held in Paris in October 2012, and to the subsequent publication of various new genes associated with albinismo, we have led the preparation, during 2013, of a large comprehensive review on this subject, engaging as co-authors all researchers currently relevant in albinism, in order to Estbaliz a new nomenclature for those new genes whose mutations are also associated with albinismo (Montoliu et al. 2014, published online in 2013). This nomenclature has been distributed and disseminated through ORPHANET, HUGO, OMIM, MGI and several other databases.

During 2013 we have also continued our activities in collaboration with associations in support of people with albinism, both in Spain, ALBA (www.albinismo.es) and in France, Genespoir (www.genespoir.org) through the participation of Lluis Montoliu, as invited speaker in their respective annual meetings, held in Huelva (April 2013) and Berck-sur-mer (France, March 2013).

Finally, during 2013 we have extended to PCT the previous patent generated on the new animal model f achromatopsia, characterized in the laboratory.

PROGRAMME:
Hereditary Cancer and Related Syndromes

Group U757

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Main lines of research

- Application of a rescue therapy in diseases associated with telomerase activity deficiency. Signalling pathways active in dyskeratosis congenita in response to DNA damage. Improve the activity of nanoparticles and lentiviral vectors for gene therapy.
- Development of a therapy base in the GSE24.2 peptide fro the treatment of short telomeres associated diseases, increase oxidative stress and geentic instability.
- Genetic diagnosis of DC y study of telomere lenght in patients of DC and idiophatic pulmonary fibrosis. Study of models of idiopathic pulmonary fibrosis using stem cells and KO mouse models for DUSP1.
- Investigation about the activity of GSE24.2 for the treatment of idiophatic pulmonary fibrosis.
- Use of GSE24.2 for the treatment of ataxia telangiectasia.

Most relevant scientific articles

- p53 pathway activation by telomere attrition in X-DC primary fibroblasts occurs in the absence of ribosome biogenesis failure and as a consequence of DNA damage. Carrillo J, González A, Manguán-García C, Pintado-Berninches L, Perona R. Clin Transl Oncol. 2013 Sep 25. [Epub ahead of print] PMID:24065372.
- Targeting Chk2 improves gastric cancer chemotherapy by impairing DNA damage repair. Gutiérrez-González A, Belda-Iniesta C, Bargiela-Iparraguirre J, Dominguez G, García Alfonso P, Perona R, Sanchez-Perez I. Apoptosis. 2013 Mar;18(3):347-60. doi: 10.1007/s10495-012-0794-2. PMID:23271172.

Highlights

GSE24.2 a peptide corresponding to an internal domain of Dyskerin (a protein member of the telomerase complex) has proved to induce telomerase activity by stabilizing hTR (The RNA component of telomerase) and increasing expression of TERT (The catalytic subunit of telomerase). GSE24.2 (Gestelmir) has been recently approved by EMA for the treatment of Dyskeratosis congenita (DC). Expression of GSE24.2 in human fibroblast is able to protect from DNA damage detected by decreased H2AX foci and ATM and CHK2 phosphorylation. Due to these findings we have explored the use of GSE24.2 in ataxia telangiectasia human cells and studied the consequences in both DNA damage and ROS production. We have used both fibroblast and lymphoblast cell lines obtained from Corriel carrying different mutation in the ATM gene. Infection of A-T human cells with lentiviral vectors expressing GSE24.2 showed a reduction in basal levels of DNA damage, decreased levels of ROS, proinflammatory cytokines, and also lower levels of p38 phosphorylation, than cells infected with control virus. Finally infection of AT cells with GSE24.2 is able to rescue these cells from senescence. We have also found that a shorter peptide than the complete GSE24.2 is also able to perfomr similar activities in Atcells. GSE24.2 and GSE4 loaded NPs could be delivered to AT and DC cells, and therefore, become an effective approach for the treatment of DC and other defective telomerase syndromes. As well as other diseases, harboring oxidative stress and inflammation.

We have cover the intellectual property of both nanoparticles and also the shorter version of the GSE24.2 peptide as well as the activities on oxidative stress and inflammation with two patents presented this year.

PROGRAMME:
Medicina Pediátrica y del Desarrollo

Group U758

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Main lines of research

- Epidemiology and risk factors in autism: Early diagnosis (screening); case-cohort studies; case-control studies.
- Epidemiology and risk factors in connective tissue diseases and autoimmune diseases: Risk factor analysis; search for drugs; quality of life; registry; costs.
- General epidemiology of rare diseases: Rare disease registry; health costs; quality of life.
- Progressive spastic paraplegia and ataxias.
- National Rare Disease Registry (SpainRDR).
- National Rare Disease Biobank (BioNER).
- National germ line mutations database (SpainMDB).
- Development of computer workflows for the analysis and interpretation of data generated by massive sequencing.
- Identification of microRNAs involved in regulating genes causing rare diseases by means of high-throughput assays with microRNA libraries.
- Genetics of retinoblastoma.
- Molecular and cellular biology of rare childhood tumors (sarcomas).

- Genetics and immunopathology of the Langerhans cell histiocytosis.
- Role of mesenchymal stem cells in imperfect osteogenesis: new therapies.
- Molecular and cellular basis for McArdle's disease and Rasmussen's encephalitis.

Most relevant scientific articles

- Bladen CL, Rafferty K, Straub V, ..., Posada M, ...,Béroud C, Lochmüller H. The TREAT-NMD Duchenne muscular dystrophy registries: conception, design, and utilization by industry and academia. Hum Mutat. 2013;34(11):1449-57. IF: 5.213 - Q1 GENETICS & HEREDITY.
- Taruscio D, Gainotti S, Mollo E, Vittozzi L, Bianchi F, Ensini M, Posada M. The current situation and needs of rare disease registries in Europe. Public Health Genomics. 2013;16(6):288-98. IF: 2.570 - Q1 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH.
- Taruscio D, Gentile AE, De Santis M, Ferrelli RM, Posada de la Paz M, Hens M et al. EUROPLAN: A Project to Support the Development of National Plans on Rare Diseases in Europe. Public Health Genomics. 2013;16(6):278-87. IF: 2.570 - Q1 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH.
- Alonso V, Villaverde-Hueso A, Hens MJ, Morales-Piga A, Abaitua I, Posada de la Paz M. Epidemiology of hereditary ataxias in Spain: hospital discharge registry and population-based mortality study. Neuroepidemiology. 2013;41(1):13-9. IF: 2.370 - Q2 PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH - CLINICAL NEUROLOGY.
- Ruiz E, Ramalle-Gómara E, Elena A, Quiñones C, Alonso V, Posada M; and on behalf of the Spain RDR Working group. Trends in systemic lupus erythematosus mortality in Spain from 1981 to 2010. Lupus. 2013 Dec 10. [Epub ahead of print]. IF: 2.783 - Q2 RHEUMATOLOGY.

Highlights

The Institute of Rare Diseases Research (IIER) is developing the project namely, SpainRDR which aims to build the National Rare Diseases Registry in Spain in collaboration with all Spanish Health Departments of the Autonomous Communities (AC), MSSSI, CREER, medical societies, FEDER, researcher networks and also some organizations from the pharma sector (ASEBIO and AELMHU). It is a project included in the IRDIRC. The IIER is also involved in other similar projects like EPIRARE, GRDR-NIH and RD-CONNECT. In the later, the IIER is responsible for designing criteria for common data elements, to standardize operating procedures and ontologies to be implemented in the future European platform for registries, biobanks and data omics. Regarding biobanks, it is in charge to define criteria to interoperate between Europe, USA and Australia biobanks.

In 2013, the IIER has been designed as leader of the National Rare Diseases Biobank, ISCIII, which is a biobank involved in the Eurobiobank consortium as a founder since 2002.

The IIER is a full member of the European project RareBestpratices, approved in the FP7 program. This project aims to define methods and guides to be applied in the development of Clinical Practice Guidelines for Rare Diseases.

The number of IIER staff has grown because of the creation of the Human Genetic Area due to a ISCIII strategic decision. This new area includes four groups with experience in inflammation and innate immunity, genetic, cellular biology and rare tumors. A diagnostic genetic unit has been also created.

The IIER director has been officially designed as a Member of the European Union Committee of Experts on Rare Diseases (EUCERD)

PROGRAMME:
Inherited Metabolic Medicine

Group U759

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Main lines of research

- Physiopathology of adrenoleukodystrophy: impact of oxidative stress in mitochondrial function, energetic homeostasis and proteolytic processes, using the mouse model developed and characterized in our laboratory and tissues of X-ALD patients.
- Treatment of adrenoleukodystrophy: preclinical tests in the mouse model and clinical trials in patients with X-ALD.
- Peroxisomal integrative genomics. Peroxisomal metabolome characterization and the organelle's evolutive origin.
- Physiopathology of Pelizaeus Merzbacher disease, metachromatic leukodystrophy and other leukodystrophies.
- Disease model of adrenoleukodystrophy in C.elegans: role of fatty acids in oxidative stress, neurodegeneration and aging.

Most relevant scientific articles

- Launay N, Ruiz M, Fourcade S, Schlüter A, Guilera C, Ferrer I, Knecht E and Pujol A*. Oxidative stress regulates UPS and immunoproteasome functioning in a mouse model of X-adrenoleukodystrophy. Brain, 2013 Mar;136(Pt 3):891-904. IF: 10.870 (D1 Neurosciences 10/252).
- López-Erauskin J, Galino J, Ruiz M, Cuezva JM, Fabregat I, Pamplona R, Ferrer I, Portero-Otín M, Fourcade S, and Pujol A*. Impaired mitochondria oxidative phosphorylation in the peroxisomal disease X-linked adrenoleukodystrophy. Human Mol Genet, 2013 Aug 15;22(16):3296-305 . IF: 7.692 (D1, Biochemistry and Molecular Biology 28/290). & Issue Cover August 15th. & Featured in MDLinx http://www.mdlinx.com/
- Morató L, Galino J, Ruiz M, Calingasan N, Starkov AA, Dumont M, Naudí A, Martínez JJ, Aubourg P, Portero-Otín M, Pamplona R, Galea E, Beal F, Ferrer I, Fourcade S and Pujol A*. Pioglitazone halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. Brain, 2013 Aug;136(Pt 8):2432-43. IF: 9.915 (D1 Neurosciences 10/252). & Research Highlightss in Nature Rev Neurology, July 16 2013 doi:10.1038/nrneurol.2013.141. & Scientific Commentary by Carlos Moraes, Brain. 2013 Aug;136(Pt 8):2339-41. & Press release of the European Human Genetics Conference on 08 June 2013, Paris France.
- López-Erauskin J, Ferrer I, Galea E and Pujol A*. Cyclophilin D as a target for antioxidants in neurodegeneration: the X-ALD case. Biol Chem, 2013 May;394(5):621-9. Invited Review. IF: 2.683 (Q3 Biochemistry and Molecular Biology 158/290).
- Singh J, Khan M, Pujol A, Baarine M, Singh I. Histone deacetylase inhibitor upregulates peroxisomal fatty acid oxidation and inhibits apoptotic cell death in abcd1-deficient glial cells. PLoS One. 2013 Jul 26;8(7):e70712. IF: 3.730 (Q1 Multidisciplinary Sciences 7/56).

Highlights

With our recent results obtained in 2013 we have managed: i) to increase the knowledge about the molecular basis and physiopathogenesis of X -ALD and, consequently, propose the inclusion of X-ALD in the growing group of secondary mitochondrial disorders; ii) to identify new therapeutic targets as cyclophilin D, ATP-synthase or mitochondrial biogenesis drivers, the Sirt1/PGC-1/PPARγ axis; iii) to identify drugs that reverse the axonal degeneration in the mouse model of the disease, such as pioglitazone and a combination of antioxidants, both findings and transferred to phase II clinical trials as well as a licensed patent and a request of orphan drug for pioglitazone (designation obtained in January 2014); iv) to develop a method for high-throughput screening of FDA approved compounds. Among the most outstanding first decile publications we include 2 Brain and 1 Human Molecular Genetics, all as last and corresponding author and with the participation of CIBERER hired researchers. Of those, 1 Brain deserved a scientific commentary, along with an outline in Nature Reviews Neurology, and the Human Molecular Genetics highlighted through a figure in the cover of the Journal on last 15 August. 2 of these publications are co-authored by other CIBERER groups and are collaborative with other CIBER. The results of pioglitazone, presented orally at the ESHG 2013 Conference, were widely reported by international media.

Also during 2013 we have participated in the exome sequencing project promoted from CIBERER and performed in CNAG with undetermined leukodystrophies, from which emerged two good candidates that we are currently being analyzed.

PROGRAMME:
Pediatric and Developmental Medicine

Group U760

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Main lines of research

- Molecular analysis and physiopathological mechanisms of Ellis-van Creveld syndrome and Weyer's acrodental dysostosis.
- Molecular analysis of cases with autosomal recessive and autosomal dominant osteogenesis imperfecta.
- Identification and characterization of new genes responsible for pediatric syndromes.

Most relevant scientific articles

- Caparrós-Martín JA, Valencia M, Reytor E, Pacheco M, Fernández M, Perez-Aytes A, Gean E, Lapunzina P, Peters H, Goodship JA, Ruiz-Perez VL. The ciliary Evc/Evc2 complex interacts with Smo and controls Hedgehog pathway activity in chondrocytes by regulating Sufu/Gli3 dissociation and Gli3 trafficking in primary cilia. Human Molecular Genetics (2013). 22(1):124-139.
- Caparrós-Martín JA, Valencia M, Pulido V, Martínez-Glez V, Rueda-Arenas I, Amr K, Farra C, Lapunzina P, Ruiz-Perez VL*, Temtamy S*, Aglan M*.*=Corresponding authors. Clinical and molecular analysis in families with autosomal recessive osteogenesis imperfecta identifies mutations in five genes and suggests genotype-phenotype correlations. Am J Med Genet A (2013). 61A:1354-69.
- Keupp K, Beleggia F, Kayserili H, Barnes AM, Steiner M, Semler O, Fischer B, Yigit G, Janda CY, Becker J, Breer S, Altunoglu U, Grünhagen J, Krawitz P, Hecht J, Schinke T, Makareeva E, Lausch E, Cankaya T, Caparrós-Martín JA, Lapunzina P, Temtamy S, Aglan M, Zabel B, Eysel P, Koerber F, Leikin S, García KC, Netzer C, Schönau E, Ruiz-Perez VL, Mundlos S, Amling M, Kornak U, Marini J, Wollnik B. Mutations in WNT1 cause different forms of bone fragility. American Journal of Human Genetics (2013). 92(4):565-74.
- Mitsushiro Nakatomi, Maria Hovorakova, Amel Gritli-Linde, Helen Blair, Kathleen McArthur, Miroslav Peterka, Hervé Lesot, Renata Peterkova, Victor L Ruiz-Perez, Judith Goodship, Heiko Peters. Evc regulates a symmetric response to Shh signaling in molar development. Journal of Dental Research (2013). 92(3):222-8.

Highlights

During 2013 we have improved our current knowledge on the biology and function of Evc and Evc2, the two proteins mutated in Ellis-van Creveld syndrome (EvC) and Weyer´s acrodental dysostosis (Weyers), and have demonstrated the molecular mechanisms that differentiate the dominant from the recessive mutations in EVC and EVC2 (Caparros-Martin et al. Hum Mol Genet 2013). We have described: i) that Evc and Evc2 form a mutually protective protein complex, that is both proteins are mutually required for maintaining their expression levels and cellular localization at the base of primary cilia; ii) that Evc/Evc2 interact with Smoothened, the main activator of Hedgehog (Hh) signalling, to mediate Gli3/Sufu dissociation and Gli3 trafficking to the end of cilia, hence promoting target gene transcription; and iii) that the dominant Evc2 variants associated with Weyers patients form stable Evc/Evc2 complexes that instead of being localized at the base of cilia are distributed along the entire organelle, indicating that localization of Evc/Evc2 at the base of cilia is critical for Hh signalling. In contrast, the large majority of Evc2 recessive variants present in EvC patients lead to non-stable Evc/Evc2 complexes.

On the other hand, in 2013 we have collaborated with international groups in the identification of WNT1 as a new gene mutated in osteogenesis imperfecta (OI)) (Keupp et al., Am J Hum Genet 2013) and through the analysis of a cohort of patients with OI we have described genotype-phenotype correlations useful in the clinic (Caparrós-Martin et al., Am J Med Genet A 2013). Finally, along with the U753, we have conducted molecular diagnosis in EvC and OI patients and have developed a NGS-based diagnostic tool to be used in the molecular diagnosis of these two diseases.

PROGRAMME:
Sensorineural Pathology

Group U761

Group Members

STAFF MEMBERS

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ASSOCIATED MEMBERS

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Cediel Algovia, Rafael
Celaya Puértolas, Adelaida
Contreras Rodríguez, Julio
de Iriarte Rodríguez, Rocío
García Alcántara, Fernando
Magariños Sánchez, Marta
Martínez Vega, Raquel
Pajares Tarancón, Mª Ángeles
Rivera Rodríguez, Teresa
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Main lines of research

- Characterization of animal and cellular models of sensorineural hearing loss.

  - Genetics. Physiopathology of IGF-I deficit using animal and cellular models. Neuroinflammatory signature and redox balance.

  - Environment-genome interaction in animal models of hereditary hearing loss subjected to environmental stress: ototoxic agents, noise and vitamin deficiency.

  - Associated with aging.

- Identification of potential therapeutic targets and hearing loss progression markers. Role of the activity of pro-inflammatory kinase p38 MAPK in auditory damage and of the loss of function of genes from the RAF (RASopathy) family.
- Testing new therapies with small molecules and stem cells in animal models of sensorineural hearing loss.
- Animal models of retinal degeneration associated with IGF-I deficit and intracellular targets.

- Delay in growth associated with mutations in IGF1 and IGF1R insulin-like growth factor 1 receptor - IGF1R (delay in growth due to resistance to insulin-like growth factor type 1 (growth impairments and intellectual disability).
- Genetic basis for and aspects clinical of hereditary angioedema type 3.
- Phenotyping of genetically modified mice within the framework of the activity conducted through the SEFALer platform.

Most relevant scientific articles

- IGF-I deficiency and hearing loss: molecular clues and clinical implications. Varela-Nieto I, Murillo-Cuesta S, Rodríguez-de la Rosa L, Lassaletta L and Contreras J. Ped. Endocrinol. Rev. Invited Review. 10:4, 460-472. 2013.
- Programmed cell senescence during embryonic development. Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, Rodríguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M, Serrano M. Cell. 21;155(5):1104-18. 2013.
- Skeletal abnormalities in insulin-like growth factor-I mouse mutants can be partially compensated for by treatment with n- and c-terminal peptides of parathyroid hormone-related protein. Rodríguez-de la Rosa L, López-Herradón A, Portal-Núñez S, Murillo-Cuesta S, Lozano D, Cediel R, Varela-Nieto I* and Esbrit P* (*Equal senior contribution) PLoS ONE. 2014. Epub 2013.
- Spanish Society of Biochemistry and Molecular Biology: celebrating 50 years. Varela-Nieto I, Rodríguez-Tarduchy G, Pajares MA, Lara C, Galindo A and Bautista JM (artículo invitado de divulgación) FEBS News 27-29, May 2013.

Highlights

Our unit studies hereditary hearing loss and ER associated with deficits in the IGF system by using animal and cell models, and working closely with clinical groups ENT specialists and allergists. To do this, we have captured national and international private and public funding. In partnership with biotech and electronic devices companies, and supported by 2 FP7 European projects, we are working on the characterization of animal models of hearing loss and its use for preclinical testing of new drug candidates (AFHELO, www.afhelo.eu/). The ITN Marie Curie, TARGEAR (www.targear.eu), which I coordinate, is focused to study hearing loss combining basic researchers with technology transfer and translational clinical research, notably the network will develop training activities for early stage researchers.

We are an international reference in the study of the actions of IGF -I, and in the study of auditory pathophysiology as indicated by: i) the co - edition of Development of the Auditory and Vestibular Systems (Elsevier, 2013); ii) the invited lectures to IGF Gordon conferences and ARO; and iii) the organization of the 50th Workshop " Inner Ear Biology" (Madrid). In addition, I am a member of the following international committees for biomedical research: BMBS -COST (from 2013), ESF- Scientific Review Group and EUROPE_PMC -Wellcome Trust.

The objective of patenting research results has meant a delay in the publication of the work done for DIGNA Biotech, Puleva and Affichem. Despite which, since 2011, we have produced a total of 21 scientific contributions and 1 outreach article. During 2013 we have helped to define: 1) the molecular basis of embryonic development of the inner ear; and 2) the deficit in IGF -I in hearing loss and growth delay. I have coordinated the "Laboratory Animal Phenotyping Network" (SEFALer - CIBERER platform) and carried out annual training activities.

PROGRAMME:
Endocrine Medicine

Associated Group U725A

Group Members

ASSOCIATED MEMBERS

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Busturia Jimeno, María Ángeles
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Rica Etxebarria, Itxaso
Vázquez San Miguel, Federico
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Lead Researcher

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Main lines of research

- Pseudohypoparathyroidism: molecular characterization of locus GNAS
- Search of new candidate genes in monogenic diabetes, neonatal diabetes, maturity onset diabetes of the young (MODY) and mitochondrial diabetes.
- Study of genes affecting sexual differentiation
- Genetic and phenotypic characterization and differential immunohistochemistry in type 1 multiple endocrine neoplasia
- Prediction and prevention of autoimmune disorders (celiac disease and diabetes)
- Genetic and phenotypic characterization of obesity
- Genetic alterations in rare diseases of endocrine origin
- Genetic alterations in Hirchsprung disease

Most relevant scientific articles

- Moran A, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R et al.. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials.Lancet. 2013 Jun 1;381(9881):1905-15.
- Fernández-Rebollo E, Lecumberri B, Gaztambide S, Martínez-Indart L, Perez de Nanclares G, Castaño L et al.. Endocrine profile and phenotype-(epi)genotype correlation in Spanish patients with pseudohypoparathyroidism.J Clin Endocrinol Metab. 2013 May;98(5):E996-1006.
- Esteva de Antonio I, Gómez-Gil E, GIDSEEN Group. Coordination of healthcare for transsexual persons: a multidisciplinary approach.Curr Opin Endocrinol Diabetes Obes. 2013 Dec;20(6):585-91.
- García Castaño A, Pérez de Nanclares G, Madariaga L, Aguirre M, Madrid A, Nadal I et al.. Genetics of type III Bartter syndrome in Spain, proposed diagnostic algorithm.PLoS One. 2013;8(9):e74673.
- Claverie-Martín F, García-Nieto V, Loris C, Ariceta G, Nadal I, Espinosa L et al.. Claudin-19 mutations and clinical phenotype in Spanish patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis.PLoS One. 2013;8(1):e53151.

Highlights

- Participation in the RENALTUBE Project about characterization of renal tubulopathies (www.renaltube.com)
- Participation in the Europen MEDIGENE Project (FP7-279171-1) about characterization of diabetes in Mediterranean populations.
- Development of projects about molecular characterization of monogenic diabetes (Basque Department of Education GV IT795-3; Basque Health Department GV 2010111185).
- Participation in international projects on diabetes prevention, either nutritional (TRIGR project-NIH 5U01HD040364-08) or about immunomodulation using antigens (Diamyd Project).
- Colaboration with the International Group of Pediatric Diabetes (Hvidore Group)
- Completion of Di@betes Study: study about the epidemiology of diabetes in Spain; completion of the Basque study about epidemiology of diabetes in the Basque Country (Basque Health Department GV2010111058)

During the development of these projects, more than 22 articles have been published in several journals, about different aspects of genetic alterations in renal tubulopathies, multiple endocrine neoplasia, monogenic diabetes, pseudohypoparathyroidism...

PROGRAMME:
Pediatric and Developmental Medicine

Linked Clinical Group

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Main lines of research

- Intelectual disability
- Congenital malformations and developmental anomalies
- Skeletal and Ectodermal dysplasias
- Cardiomyopathies
- Lisosomal storage diseases
- Acute intermittent porphyiria
- Advanced therapies

Most relevant scientific articles

- Luxán G, Casanova JC, Martínez-Poveda B, Prados B, D'Amato G, MacGrogan D, González-Rajal A, Dobarro D, Torroja C, Martínez F, Izquierdo-García JL, Fernández-Friera L, Sabater-Molina M, Kong YY, Pizarro G, Ibañez B, Medrano C, García-Pavía P, Gimeno JR, Monserrat L, Jiménez-Borreguero LJ, de la Pompa JL. Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy. Nat Med. 2013 Feb;19(2):193-201. doi: 10.1038/nm.3046. Epub 2013 Jan 13. (FI: 24.302).
- O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E,Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; for the Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J. 2013 Oct 14. [Epub ahead of print](FI: 14.097).
- Wieczorek D, Bögershausen N, Beleggia F, Steiner-Haldenstätt S, Pohl E, Li Y, Milz E, Martín M, Thiele H, Altmüller J, Alanay Y, Kayserili H, Klein-Hitpass L, Böhringer S, Wollstein A, Albrecht B, Boduroglu K, Caliebe A, Chrzanowska K, Cogulu O, Cristofoli F, Czeschik JC, Devriendt K, Dotti MT, Elcioglu N, Gener B, Goecke TO, Krajewska-Walasek M, Guillén-Navarro E, Hayek J, Houge G, Kilic E, Simsek-Kiper PÖ, López-González V, Kuechler A, Lyonnet S, Mari F, Marozza A, Mathieu Dramard M, Mikat B, Morin G, Morice-Picard F,

Ozkinay F, Rauch A, Renieri A, Tinschert S, Utine GE, Vilain C, Vivarelli R, Zweier C, Nürnberg P, Rahmann S, Vermeesch J, Lüdecke HJ, Zeschnigk M, Wollnik B. A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. Hum Mol Genet. 2013 Dec 20;22(25):5121-35. doi: 10.1093/hmg/ddt366. Epub 2013 Aug 1. (FI:7.69).

- Guillén-Navarro E, Sánchez-Iglesias S, Domingo-Jiménez R, Victoria B, Ruiz-Riquelme A, Rábano A, Loidi L, Beiras A, González-Méndez B, Ramos A, López-González V, Ballesta-Martínez MJ, Garrido-Pumar M, Aguiar P, Ruibal A, Requena JR, Araújo-Vilar D. A new seipin-associated neurodegenerative síndrome. J Med Genet. 2013 Jun;50(6):401-9. doi: 10.1136/jmedgenet-2013-101525. (FI: 5.7).
- Vera-Carbonell A, López-González V, Bafalliu JA, Piñero-Fernández J, Susmozas J, Sorli M, López-Pérez R, Fernández A, Guillén-Navarro E, López-Expósito I. Pre- and postnatal findings in a patient with a novel rec(8)dup(8q)inv(8)(p23.2q22.3) associated with San Luis Valley syndrome. Am J Med Genet A. 2013 Sep;161(9):2369-75. doi: 10.1002/ajmg.a.36103. Epub 2013 Jul 25.

Highlights

RESEARCH GRANTS

- "Clinical phenotype and molecular mechanism of a new neurodegenerative síndrome associated to R265X mutation in the seipin gene". FIS PI10/02873. From 2010 to 2013. Funding: 102.850,00 euros. PI: Jesús Requena. CI: MR Domingo Jiménez and E Guillén Navarro.
- "From the channel to the classical arrhythmia. Clinical, genetics and functional study of channelopathies". FIS. PI11/02459. From 2012 to 2014. Funding: 56.000 euros. PI: Juan Ramón Gimeno Blanes
- "Genetic approach to the Rett síndrome and its variants: clinical and molecular characterization of the overlapping neuropsychiatrics phenotypes" Departamento de Sanidad del Pais Vasco. Fundación vasca de Innovación e Investigación sanitarias. Project number: 2011111090. From 2012 to 2015. Funding: 61.500,00 euros. PI: M. Isabel Tejada; CI: E Guillén Navarro and MR Domingo Jiménez

CLINICAL TRIALS

- A randomized, double blind, 12-week, parallel group, placebo-controlled study of the efficacy and safety of RO4917523 in patients with Fragile X Syndrome. NP27936. Sponsor: F-Hoffmann-La Roche, LTD.
- Ranol-MCH "Effect study of Ranolazine in the myocardial ischemic in patients with hypertrophic cardiomyopathy" Sponsor: Menarini. EPA-SP. RGB-RAN 2013-01.
- "Tolerance and safety of dronedarone and other antiarrhythmic treatment of atrial fibrillation in hypertrophic cardiomyopathy". Sponsor: Sanofi.

ORGANIZED ACTIVITIES

- Annual Meeting of the Working group of Family Heart Disease of the Spanish Society of Cardiology. 22-23 March 2013 Hotel Silken Siete Coronas. Murcia.
- II Cardiogenetic day. 29 November 2013 Hospital Universitario Virgen de la Arrixaca. Accredited by University Hospital Virgen de la Arrixaca and University of Murcia.
- Achondroplasia and Motherhood day. University Hospital Virgen de la Arrixaca. Murcia, December 5, 2013.

CLINICAL PRACTICE GUIDELINES

- Guillén-Navarro E, Blasco AJ, Gutierrez-Solana LG, Couce ML, Cancho-Candela R, Lázaro P; grupo de trabajo Hunter España. [Clinical practice guideline for the management of Hunter syndrome]. Med Clin (Barc). 2013 Nov 16;141(10):453.e1-13. doi: 10.1016/j.medcli.2013.07.010. Epub 2013 Sep 21. Presentación: Hotel Abba Garden. Barcelona September 3rd 2013.

BOOK CHAPTER

- Guillén-Navarro E. What is the achondroplasia and how is it diagnosed? In: Guillén-Navarro E, Hernández Morcuende I, Conejero Casares A, González Viejo MA. I have a child with achondroplasia and now what?. Asociación Crecer (eds). Diciembre de 2013. Murcia. ISBN: 84-695-8637-8; pp.7-13

PROGRAMME:
Pediatric and Developmental Medicine

Linked Clinical Group

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Main lines of research

- Cornelia de Lange Syndrome and Cohesinopathies (main).
- Intellectual Disability of Genetic Origin: Fragile X Syndrome.
- Innborn Errors of Metabolism: HMG-CoA Lyase Deficiency.
- Short stature and overgrowth syndromes.
- Genetic Hearing Loss.
- Paediatric Dysmorphic Syndromes.
- Genetic Neuromuscular Diseases in Childhood.

Most relevant scientific articles

- Loss-of-function HDAC8 mutations cause a phenotypic spectrum of Cornelia de Lange syndrome-like features, ocular hypertelorism, large fontanelle and X-linked inheritance. Kaiser FJ, Ansari M, Braunholz D, Concepción Gil-Rodríguez M, Decroos C, Wilde JJ, Fincher CT, Kaur M, Bando M, Amor DJ, Atwal PS, Bahlo M, Bowman CM, Bradley JJ, Brunner HG, Clark D, Del Campo M, Di Donato N, Diakumis P, Dubbs H, Dyment DA, Eckhold J, Ernst S, Ferreira JC, Francey LJ, Gehlken U, Guillén-Navarro E, Gyftodimou Y, Hall BD, Hennekam R, Hudgins L, Hullings M, Hunter JM, Yntema H, Innes AM, Kline AD, Krumina Z, Lee H, Leppig K, Lynch SA, Mallozzi MB, Mannini L, McKee S, Mehta SG, Micule I; Care4Rare Canada Consortium, Mohammed S, Moran E, Mortier GR, Moser JA, Noon SE, Nozaki N, Nunes L, Pappas JG, Penney LS, Pérez-Aytés A, Petersen MB, Puisac B, Revencu N, Roeder E, Saitta S, Scheuerle AE, Schindeler KL, Siu VM, Stark Z, Strom SP, Thiese H, Vater I, Willems P, Williamson K, Wilson LC; University of Washington Center for Mendelian Genomics, Hakonarson H, Quintero-Rivera F, Wierzba J, Musio A, Gillessen-Kaesbach G, Ramos FJ, Jackson LG, Shirahige K, Pié J, Christianson DW, Krantz ID, Fitzpatrick DR, Deardorff MA. Hum Mol Genet. 2014 Jan 31. [Epub ahead of print] PMID: 24403048 [PubMed - as supplied by publisher].
- Somatic mosaicism in a Cornelia de Lange syndrome patient with NIPBL mutation identified by different next generation sequencing approaches. Baquero-Montoya C, Gil-Rodríguez MC, Braunholz D, Teresa-Rodrigo ME, Obieglo C, Gener B, Schwarzmayr T, Strom TM, Gómez-Puertas P, Puisac B, Gillessen-Kaesbach G, Musio A, Ramos FJ, Kaiser FJ, Pié J. Clin Genet. 2014 Jan 26. doi: 10.1111/cge.12333. [Epub ahead of print] No abstract available. PMID: 24635725 [PubMed - as supplied by publisher].

- Could a patient with SMC1A duplication be classified as a human cohesinopathy? Baquero-Montoya C, Gil-Rodríguez MC, Teresa-Rodrigo ME, Hernández-Marcos M, Bueno-Lozano G, Bueno-Martínez I, Remeseiro S, Fernández-Hernández R, Bassecourt-Serra M, Rodríguez de Alba M, Queralt E, Losada A, Puisac B, Ramos FJ, Pié J. Clin Genet. 2014 May;85(5):446-51. doi: 10.1111/cge.12194. Epub 2013 Jun 17. PMID: 23683030 [PubMed - in process].
- Cornelia de Lange syndrome with NIPBL mutation and mosaic Turner syndrome in the same individual. Wierzba J, Gil-Rodríguez MC, Polucha A, Puisac B, Arnedo M, Teresa-Rodrigo ME, Winnicka D, Hegardt FG, Ramos FJ, Limon J, Pié J. BMC Med Genet. 2012 Jun 7;13:43. PMID: 22676896 [PubMed - indexed for MEDLINE].
- Mutations and variants in the cohesion factor genes NIPBL, SMC1A, and SMC3 in a cohort of 30 unrelated patients with Cornelia de Lange syndrome. Pié J, Gil-Rodríguez MC, Ciero M, López-Viñas E, Ribate MP, Arnedo M, Deardorff MA, Puisac B, Legarreta J, de Karam JC, Rubio E, Bueno I, Baldellou A, Calvo MT, Casals N, Olivares JL, Losada A, Hegardt FG, Krantz ID, Gómez-Puertas P, Ramos FJ. Am J Med Genet A. 2010 Apr;152A(4):924-9. doi: 10.1002/ajmg.a.33348. PMID: 20358602 [PubMed - indexed for MEDLINE].

Highlights

PROJECTS:

Project FIS "Cornelia de Lange Spectrum: New genes, new phenotypes and therapeutic approach." Type Ref: PS12 / 01318. Funding Agency: Ministry of Health and Social Policy. FIS. Duration: 2013-2015. Lead Researcher: Feliciano J. Ramos-Fuentes. 1st year: 2 publications in progress.

PUBLICATIONS:

Three (3) papers were finished and finally published in 2014 (see above).

CLINICAL GUIDES:

The "Clinical Utility Gene Card of Cornelia de Lange Syndrome" is expected to be published in 2014 in the European Journal of Human Genetics.

CONGRESSES: Conferences by invitation and papers were presented on 3 Conferences:

- ESHG Conference (Paris, June 2013).
- VIII Spainish Congress of Cornelia de Lange Syndrome (Barcelona, Spain October 2013).
- 7th Cornelia de Lange Syndrome World Conference (Buenos Aires, November 2013).

PROGRAMME:
Pediatric and Developmental Medicine

Linked Clinical Group

Group Members

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Main lines of research

- Mental retardation.
- Sudden death.
- Congenital Heart Disorders.
- Childhood epilepsy.
- Neuromuscular, neurometabolic and neurodevelopmental disorders.
- Multiple mieloma.
- Etc.

Most relevant scientific articles

- Sánchez-Ferrero E, Coto E, Beetz C, Gámez J, Corao AI, Díaz M, Esteban J, del Castillo E, Moris G, Infante J, Menendez M, Pascual-Pascual SI, López de Munain A, García-barcina MJ, Alvarez V; Genetics of Spastic Paraplegia study group. " SPG7 mutational screening in spastic paraplegia patients supports a dominant effect for some mutations and a pathogenic role for p.A510V". Clin Genet 2013 Mar; 85(3): 252-262.
- Flaquer A, Baumbach C, Piñero E, García Algas F, de la Fuente Sanchez MA, Rosell J; Toquero J, Alonso-Puilpon L, García –Pavia P, Strauch K, Heine Suñer D. " Genome-wide linkage analysis of congenitla heart defects using MOD score analysis identifies two novel loci". BMC Genet 2013 May 24; 14:44. Doi: 10.1186/1471-2156-14-44.
- Aldámiz-Echevarria L, Bueno MA, Couce ML, Lage S, dalmau J, Vitoria I, Andrade F, Blasco J, Alcalde C, Gil D, García MC, González Lamuño D, Ruiz M, Peña-Quintana L, Ruiz MA, González D, Sánchez-Valverde F. "Anthropometric characteristics and nutrition ina cohort of PAH-deficient patients". Clin Nutr 2013 Sep 26. pii: S0261-5614 (13)00249-5. Doi: 10.1016/j.clnu.2013.09.011.
- Suarez-Calvet M, Dols-Icardo O, Lladó A, Sanchez-Valle R, Hernández I, Amer G, Antón-Aguirre S, Alcolea D, Fortea J, Ferrer I, van der Zee J, Dillen L, Van Broeckhoven C, Molinuevo JL, Blesa R, Clarimón J, Lleó A. "Plasma phosphorylated TDP-43 levels are elevated in patients with frontotemporal dementia carrying repeat expansión or a GRN mutation". J Neurol Neurosurg Psychiatry, 2013 Dec 4. Doi: 10.1136/jnnp-2013-305972.

Highlights

The GCV achieved to pass the evaluation of the Health Research Foundation of the Balearic Islands (FISIB) as Consolidated Research Group (PI: Jordi Rosell) in August 2013.

The course "Genètica Avui" held in March by Genetics Unit was a great success with a great number of participants.

The highlight in 2013 of the GCV :

Today we are in the final validation of the study of 69 adult patients, which were hospitalized in a public daycare and never have been examined from a genetically point of view. The study by aCGH was diagnostic in 10% of the patients, and was normal in 50% (34 patients). Two patients more were diagnosed by FISH and molecular methods of del22q11 and Cornelia de Lange syndromes. In the remaining patients we detected VOUS and are now in the phase of family study and final validation.

It has continued the pilot carrier of Fragile X syndrome study with preliminary results which may lead to changes in diagnostic methodology in this disease. In the ambit of this disease, the University Hospital Espases has launched the Multidisciplinary Clinical Monitoring Unit of patients with Fragile X syndrome.

The Metabolic Neurology group participates in the development of therapeutic guide in Mucopolysaccharidosis type I and the Neuropediatric group in the epidemiological study to assess the severity of RSV infection in patients with severe neurological disease (SENEP -EPI - 2013-01) .

It has also awared our group with a FIS project (PI: Damia Heine): "Determination of the genetic and molecular basis of congenital heart defects through family studies and animal models"

PROGRAMME:
Pediatric and Developmental Medicine

Linked Clinical Group

Group Members

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Main lines of research

- Intellectual disability, particularly X-linked, fragile X syndrome and pathologies associated with the spectrum of Rett syndrome
- Dysmorphology
- Hereditary Cancer
- Neurological diseases
- Advanced therapies
- Etc.

Most relevant scientific articles

- Trisomy 18p caused by a supernumerary marker with a chromosome 13/21 centromere: a possible recurrent chromosome aberration. Plaja A, Lloveras E, Martínez-Bouzas C, Barreña B, Del Campo M, Fernández A, Herrero M, Barranco L, Palau N, López-Aríztegui MA, Català V, Tejada MI. Am J Med Genet A. 2013 Sep;161(9):2363-8. doi: 10.1002/ajmg.a.36102. Epub 2013 Jul 25.
- [Clinical guideline of gene FMR1-associated diseases: fragile X syndrome, primary ovarian insufficiency and tremor-ataxia syndrome]. Milá M, Ramos F, Tejada MI; Group AEGH/CIBERER. Med Clin (Barc). 2014 Mar 4;142(5):219-25. doi: 10.1016/j.medcli.2013.05.025. Epub 2013 Jul 25. Spanish. No abstract available.

- MECP2 gene study in a large cohort: testing of 240 female patients and 861 healthy controls (519 females and 342 males). Maortua H, Martínez-Bouzas C, García-Ribes A, Martínez MJ, Guillen E, Domingo MR, Calvo MT, Guitart M, Gabau E, Botella MP, Gener B, Rubio I, López-Arízteguí MA, Tejada MI. J Mol Diagn. 2013 Sep;15(5):723-9. doi: 10.1016/j.jmoldx.2013.05.002. Epub 2013 Jun 26.
- Assessment of interferon-related biomarkers in Aicardi-Goutières syndrome associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, and ADAR: a case-control study. Rice GI, Forte GM, Szynkiewicz M, Chase DS, Aeby A, Abdel-Hamid MS, Ackroyd S, Allcock R, Bailey KM, Balottin U, Barnerias C, Bernard G, Bodemer C, Botella MP, Cereda C, Chandler KE, Dabydeen L, Dale RC, De Laet C, De Goede CG, Del Toro M, Effat L, Enamorado NN, Fazzi E, Gener B, et al. Lancet Neurol. 2013 Dec;12(12):1159-69. doi: 10.1016/S1474-4422(13)70258-8. Epub 2013 Oct 30.
- A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. Wieczorek D, Bögershausen N, Beleggia F, Steiner-Haldenstätt S, Pohl E, Li Y, Milz E, Martín M, Thiele H, Altmüller J, Alanay Y, Kayserili H, Klein-Hitpass L, Böhringer S, Wollstein A, Albrecht B, Boduroglu K, Caliebe A, Chrzanowska K, Cogulu O, Cristofoli F, Czeschik JC, Devriendt K, Dotti MT, Elcioglu N, Gener B, et al. Hum Mol Genet. 2013 Dec 20;22(25):5121-35. doi: 10.1093/hmg/ddt366. Epub 2013 Aug 1.

Highlights

RESEARCH PROJECTS:

The two most important were:

- Genetic study of primary ovarian insufficiency in follicular cells in young women carriers of premutation of the fragile X syndrome: correlation with clinical parameters. PI: Tejada MI. FIS-Reference: PI10/00550.
- Genetic approach to Rett syndrome and its variants: clinical and molecular characterization of phenotypes that overlap. PI: Tejada MI. Basque Government-Reference: 2011111090.

RESULTS:

The most important results were published (see previous section) or in press, having been presented in the following national and international meetings:

- Exome sequencing application to decipher the gene responsible for the MRX82 family: a unique UPF3B gene mutation produces a variety of phenotypes. Tejada MI, et al. XXVII National Congress of the Spanish Association of Human Genetics. Madrid 10-12 April 2013.
- Study of triple CGG repeats (FMR1 gene) in 157 patients with ovarian failure of unknown origin. Tejada MI, et al. European Human Genetics Conference 2013. Paris 8-11 June 2013.
- Study of triple CGG repeats and AGG interruptions in 41 low-responder women with a reduced ovarian response in ISCI program: A preliminary study on the comparison between blood and granulosa cells. Tejada MI, et al. The 1st International Conference on the FMR1 premutation: basic mechanisms and clinical involvement. Perugia (Italy) 23-26 June 2013.
- Study of triple CGG repeats (FMR1 gene) in 41 patients with a reduced ovarian response to gonadotropin stimulation: no correlation found with four ovarian parameters. Tejada MI, et al. European Society of Human Reproduction and Embryology (ESHRE) 7-10 July 2013. London

CLINICAL GUIDELINES:

The aforementioned in the publications' section.

CLINICAL TRIALS:

Authorization by the AEM (Spanish Agency of medicines) in August 2013 of the trial: Cell therapy, mesenchymal stem cells-based, applied to pediatric patients with Osteogenesis Imperfecta (TERCELOI). Reference: EC10-219. Clinical Coordinator: Blanca Gener.

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